



Honey We Shrunk the Omnicef: 3rd Generation Cephalosporin Stewardship

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Question...

- If you could, instantly, delete one antibiotic from existence, which antibiotic would you select?

1. Vancomycin
2. Piperacillin-tazobactam
3. Ceftazidime
4. Cefepime
5. Metronidazole
6. Ceftriaxone
7. Cefdinir
8. Others



Pediatric 1st Line Antibiotics

Infection	Intravenous	Oral
Community-acquired Pneumonia	Ampicillin	Amoxicillin
Pyelonephritis	Ceftriaxone	Cephalexin
Cystitis	Cefazolin	Cephalexin
Acute Otitis Media	NA	Amoxicillin
Bacterial Sinusitis	NA	Amoxicillin-clavulanate
GAS Pharyngitis	NA	Amoxicillin

We use narrow-spectrum, β -lactams

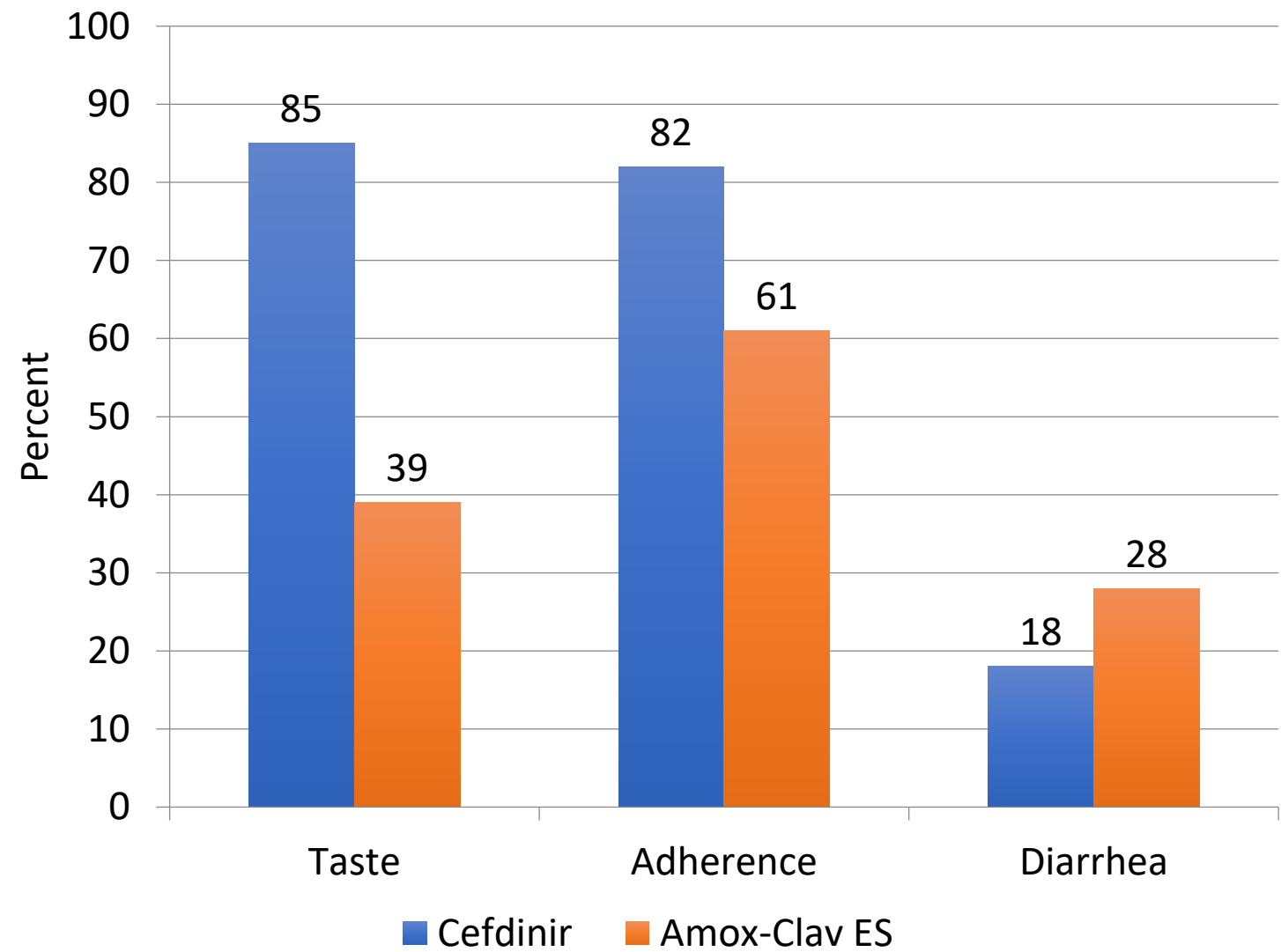
Why Target 3rd Generation Cephalosporins (3GC)?

- **Broad-spectrum compared to amoxicillin and cephalexin**

Why Target 3rd Generation Cephalosporins (3GC)?

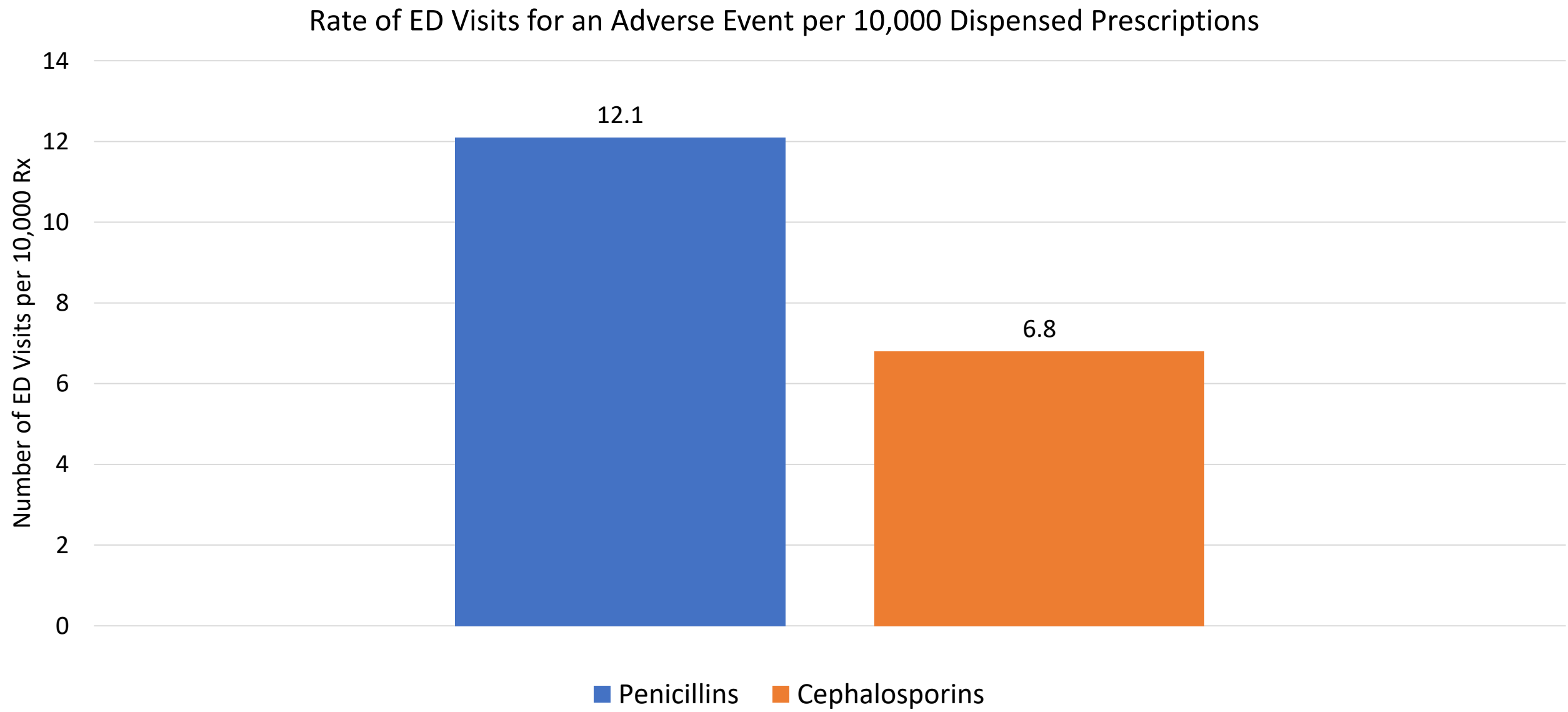
- Broad-spectrum compared to amoxicillin and cephalexin
- **Ease of use makes them overused**

Cefdinir vs Amoxicillin-Clavulanate in Otitis Media



Study Design	<ul style="list-style-type: none">• Multicenter• Investigator blinded• 6 month – 6-years old
Intervention	<ul style="list-style-type: none">• Amox-Clav ES 45 mg/kg q12h• Cefdinir 7 mg/kg q12h

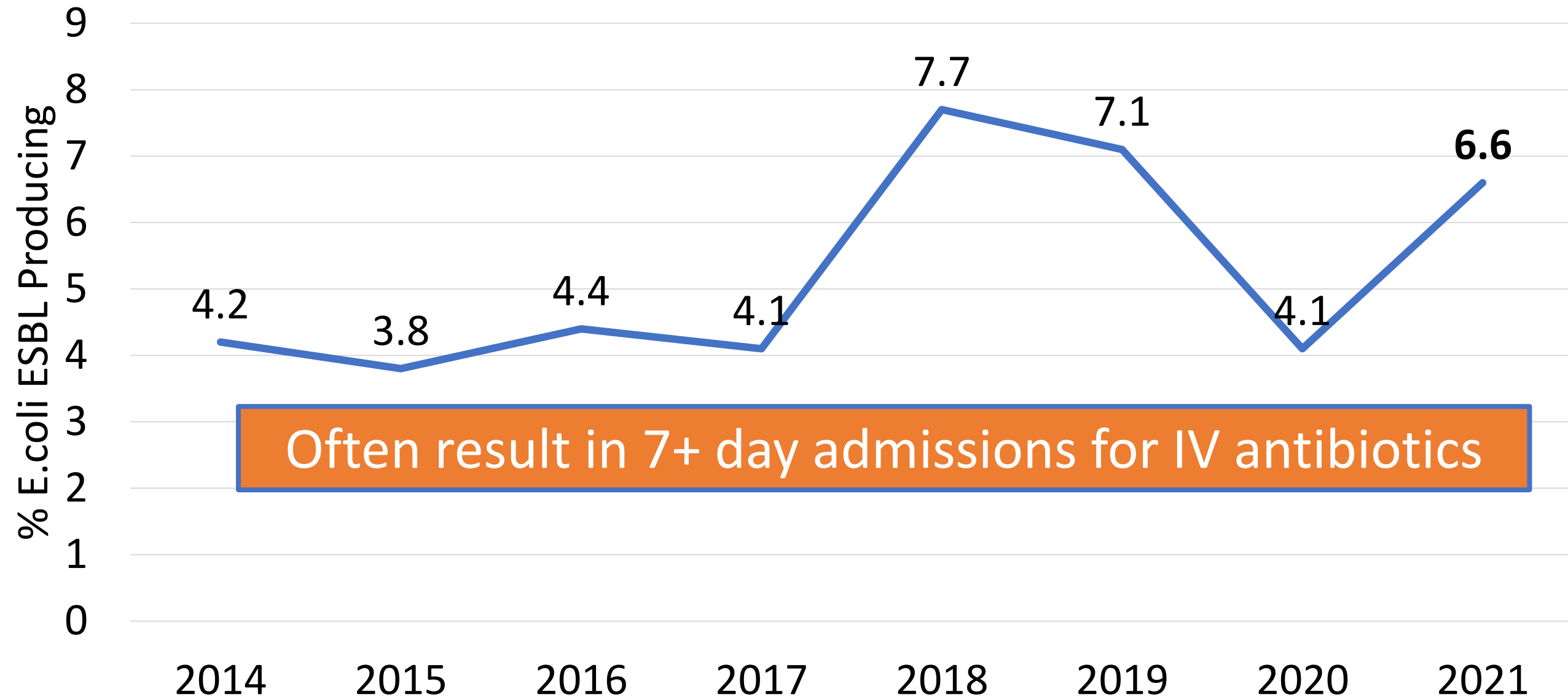
Adverse Effects in Children from Antibiotics



Why Target 3rd Generation Cephalosporins (3GC)?

- Broad-spectrum compared to amoxicillin and cephalixin
- Ease of use makes them overused
- **Decrease extended spectrum β -lactamase (ESBL) producing organisms**

CHNO ESBL E.coli Trends



Why Target 3rd Generation Cephalosporins (3GC)?

- Broad-spectrum compared to amoxicillin and cephalexin
- Ease of use makes them overused
- Decrease extended spectrum β -lactamase (ESBL) producing organisms
- **Oral 3GC are relatively expensive**
 - Across Children's facilities, 3861 Rx for cefdinir in 2021 → Average wholesale of ~\$411,662
 - Amoxicillin and cephalexin are 20-90% cheaper depending on formulation

Why Target 3rd Generation Cephalosporins (3GC)?

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- Oral 3GC are relatively expensive
 - Across Children's facilities, 3861 Rx for cefdinir in 2021 → Average wholesale of ~\$411,662
 - Amoxicillin and cephalexin are 20-90% cheaper depending on formulation
- **Incorrect interpretation of susceptibility for oral 3GC (and efficacy)**
 - Extrapolate from penicillin for *S.pneumoniae*
 - Extrapolate from cefazolin for *E.coli*

Streptococcus Pneumoniae Susceptibilities

- *Streptococcus pneumoniae* antibiotic susceptibilities to β -lactams can be tested directly or extrapolated from penicillin testing
- **Example of extrapolation**
 - Amoxicillin is extrapolated from a penicillin MIC ≤ 2
 - Cefdinir is extrapolated from a penicillin MIC of ≤ 0.06
- **Example of direct testing**
 - Ceftriaxone is predicted to be susceptible with an MIC of ≤ 1
 - Cefdinir is predicted to be susceptible with an MIC of ≤ 0.5

S.pneumoniae Susceptibilities at CHNO since 2020

Drug	MIC Determination	CHNO Susceptibilities
Amoxicillin	Penicillin MIC ≤ 2	94%
Ceftriaxone	MIC ≤ 1	99%

Can You Extrapolate Cefdinir from Cefotaxime?

Cefotaxime MIC (µg/ml)	Cefdinir MIC (µg/ml)									
	<0.03	0.03	0.06	0.12	0.25	0.5	1	2	4	>4
<0.03	9		62	16	2					
0.03		6	50	4	2					
0.06	1		3	5	9	1				
0.12		1	1	2	2	4				
0.25					2	1	1	1		
0.5							3	9	14	
1								1	20	7
2										4
4										1
>4										4

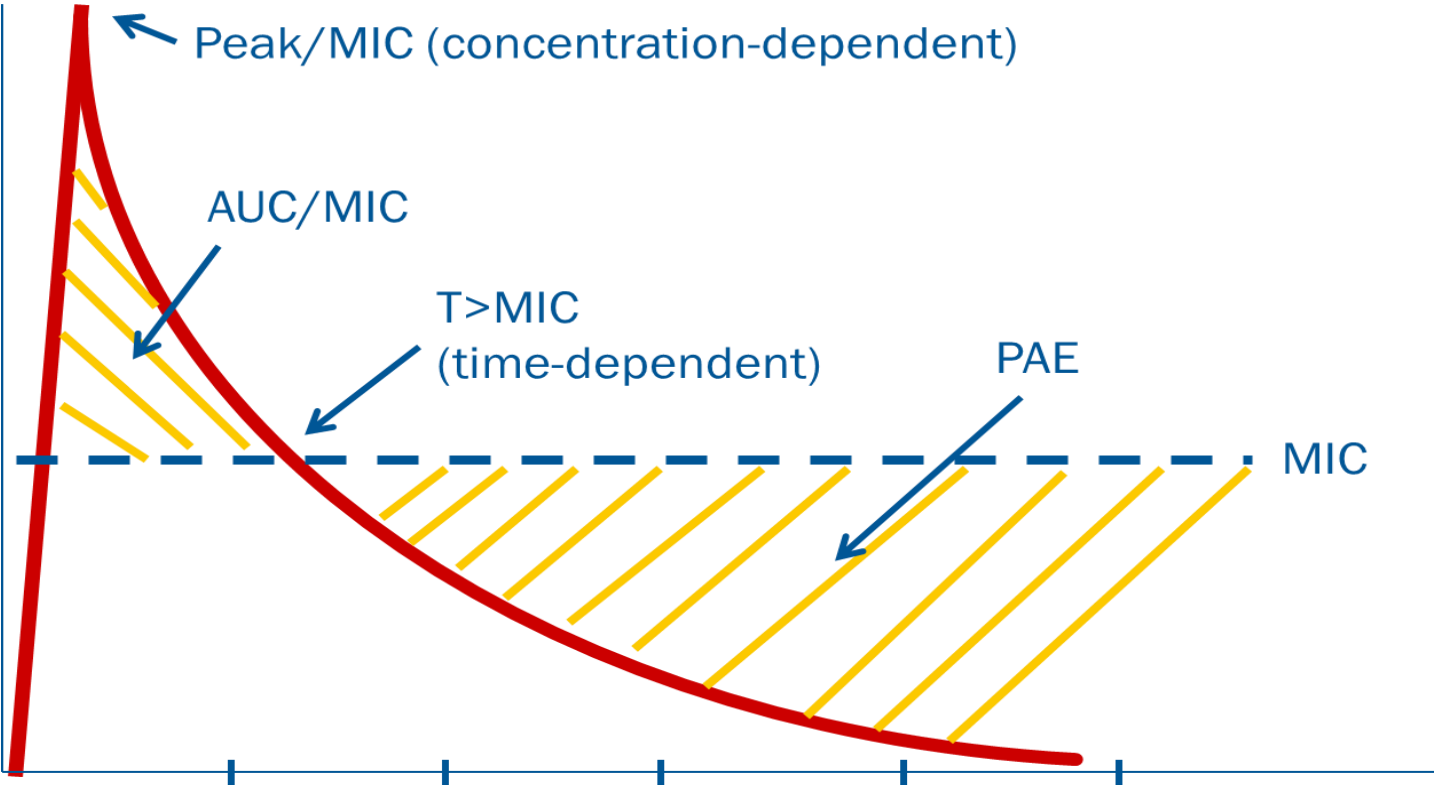
S.pneumoniae Susceptibilities

Drug	MIC Determination	CHNO Susceptibilities
Amoxicillin	Penicillin MIC ≤ 2	94%
Ceftriaxone	MIC ≤ 1	99%
Cefdinir	Penicillin MIC ≤ 0.06	44%
Cefdinir	Cefotaxime MIC < 0.25	8-49%



Cefdinir resistance with MICs of 0.25 and above, only 5 isolates at CHNO had MICs this low since 2020

Antimicrobial PK/PD Parameters – $T > MIC$



Antimicrobial	PD-PK Parameter
Aminoglycoside	Peak/MIC
Fluoroquinolone	AUC/MIC
Vancomycin	AUC/MIC
Beta-Lactams	T > MIC
Azole	AUC/MIC
Metronidazole	Peak/MIC
Clindamycin	AUC/MIC

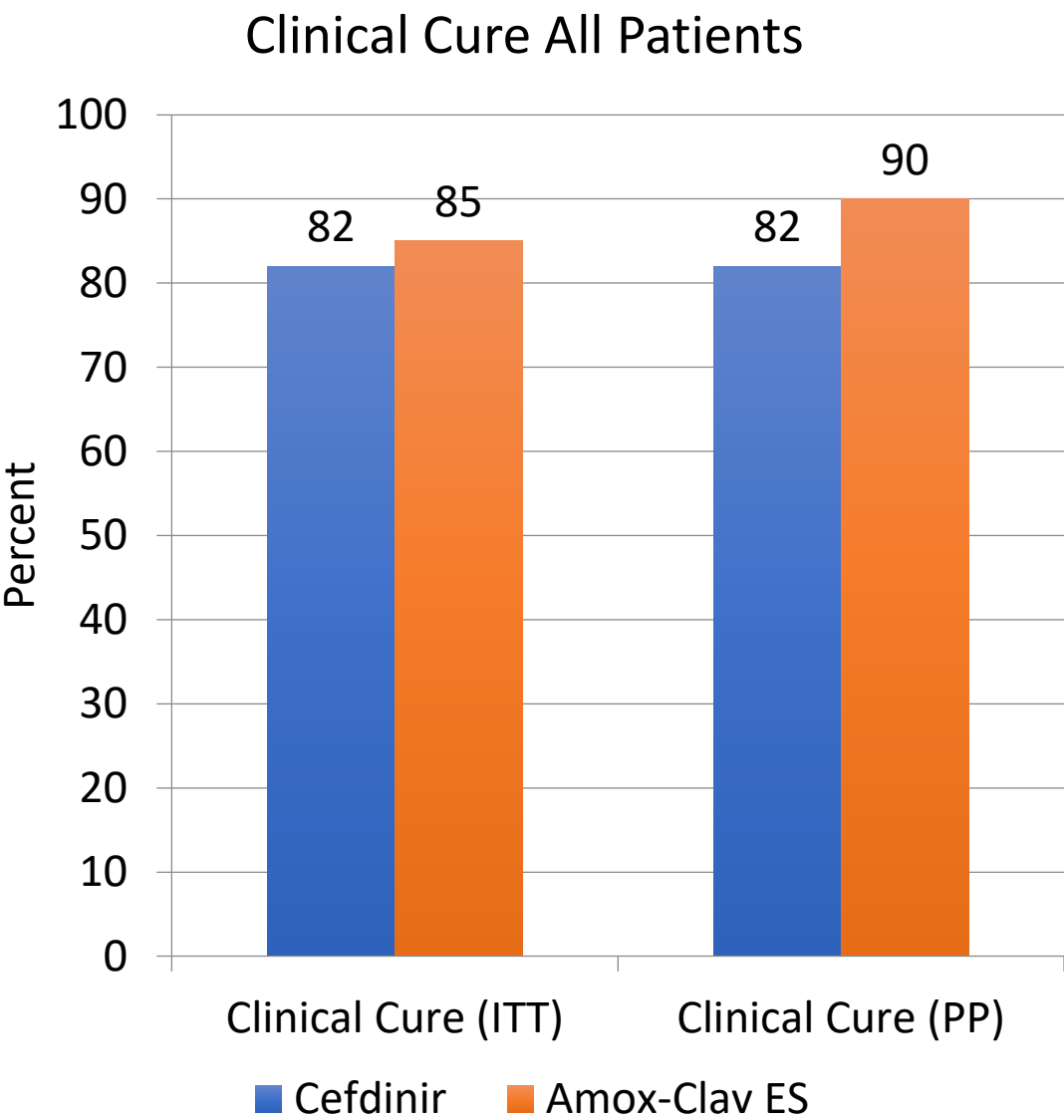
AUC – area under the curve, MIC – minimum inhibitory concentration, T – time, PD – Pharmacodynamic, PK – pharmacokinetic

Up the Dose?

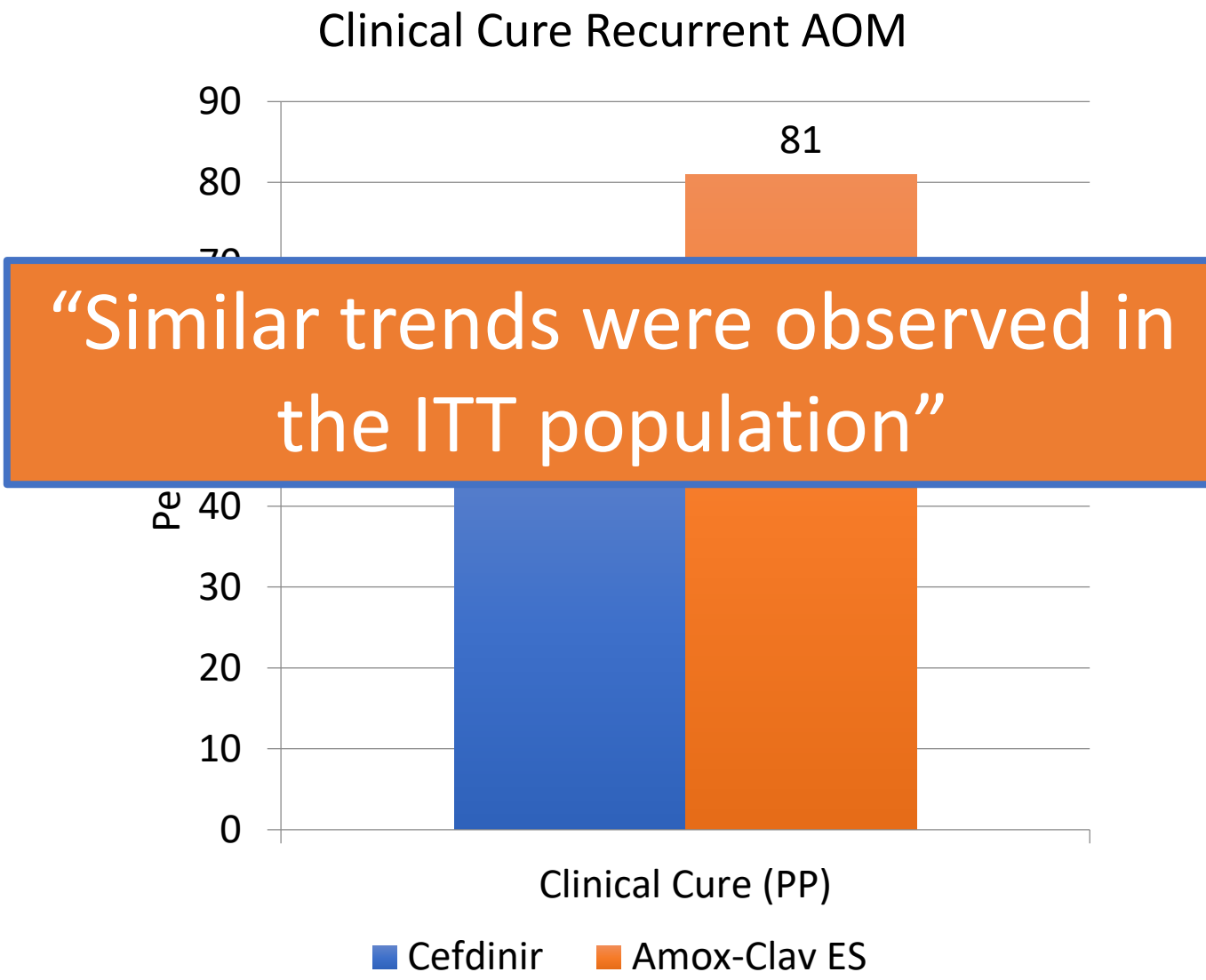
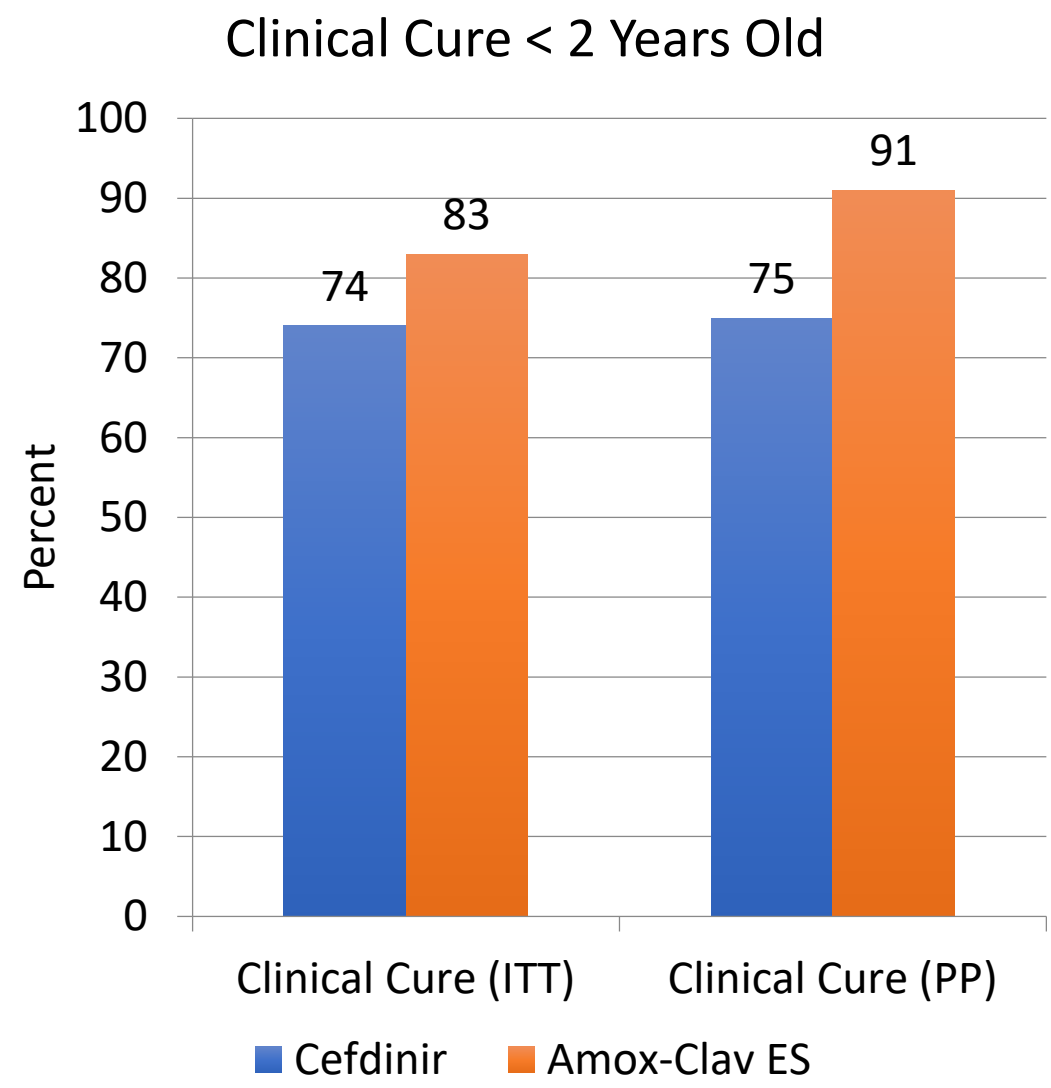
Percentage of Time > MIC for Cefdinir and Streptococcus pneumoniae			
Dose	Susceptible	Intermediate	Resistant
14 mg/kg daily	42	23	13
14 mg/kg Q12H	80	48	31
25 mg/kg daily	47	30	21
25 mg/kg Q12H	82	61	44

Cefdinir vs Amoxicillin-Clavulanate in Otitis Media

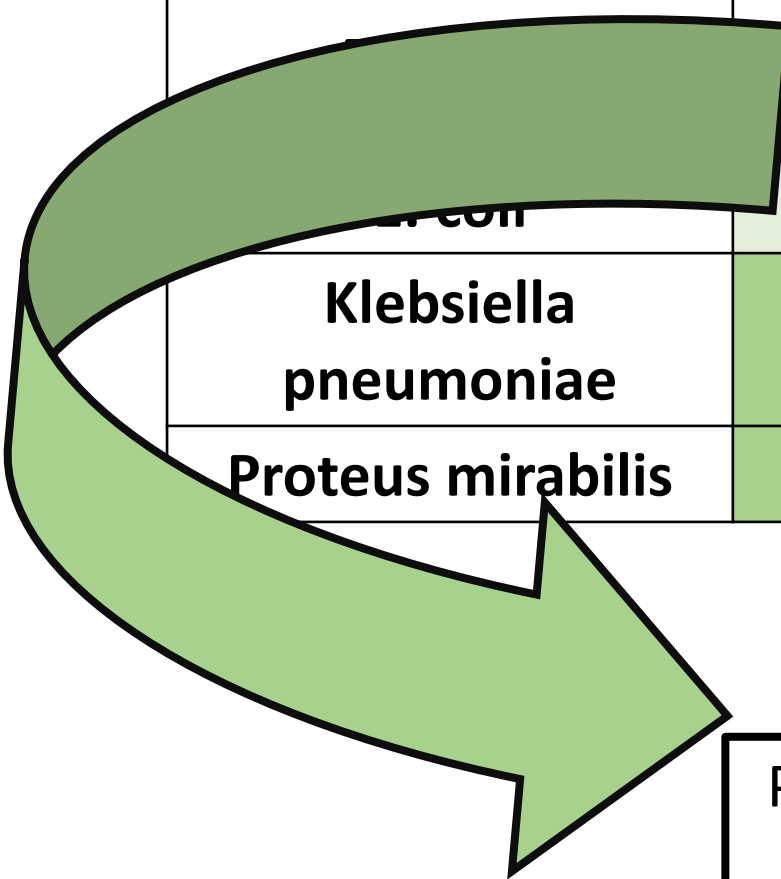
Study Design	<ul style="list-style-type: none">MulticenterInvestigator blinded6 month – 6-years old
Intervention	<ul style="list-style-type: none">Amox-Clav ES 45 mg/kg q12hCefdinir 7 mg/kg q12h
Results	<ul style="list-style-type: none">Cefdinir worse for recurrence (p=.01)Cefdinir worse for < 24 months (p=.04)



Cefdinir vs Amoxicillin-Clavulanate in Otitis Media



Sensitivities for Urine Organisms



	Cefazolin (urine) Determines Cephalexin & Cefdinir	Ceftriaxone	Sulfamethoxazole Trimethoprim
Staphylococcus aureus	84	93	68
Klebsiella pneumoniae	95	97	86
Proteus mirabilis	100	100	91

PO 3rd gen cephalosporins
have drastically different
kinetics than ceftriaxone

**PO 3rd Gen Cephalosporins
≠ Ceftriaxone**

Cefdinir vs Cephalexin for UTIs

	Cephalexin	Cefdinir	Ceftriaxone
Generation	1 st Generation	3 rd Generation	3 rd Generation
Oral Absorption	90%	25%	N/A
Protein Binding	5-15%	60-70%	85-95%
Half-life	1 hour	1.7 hours	8 hours
Urinary Elimination	90%	7-25%	33-67%
Susceptibility Surrogate	Cefazolin with MIC of ≤ 16	Cefazolin with MIC of ≤ 16	Tested directly
Dosing	Q8h preferred	Q12h	Q24h

The Start of a Stewardship Program

- Local Antimicrobial Stewardship Program (ASP) Guidelines created in conjunction with hospitalist team for:
 - Inpatient Community-acquired Pneumonia
 - Inpatient Urinary Tract Infection
- Local Clinical Guidelines Committee (CGC) in conjunction with ASP created guidelines for:
 - Community-acquired Pneumonia in the Emergency Department
 - Urinary Tract Infection in the Emergency Department

Consensus Guideline
between ASP & Non-
ASP Departments

PDF added to EPIC
Resources and annually
to Antimicrobial
Handbook

Order-Panel created to
streamline EPIC
ordering and guideline
adherence

Education sessions
depending on project

Add Order-Panel to
“Inpatient Antimicrobial
Order-set”

Update admission
order-set if available

Track %
antimicrobials
ordered via
order-set or
panel as
metric

Improved
reliability in ID
care

Increased volume of content increases “Ctrl+F”
or searchability of Handbook

Allows us to streamline education for residents
“use the order-set” vs “use one of the 10+ order-
panels you must remember we have”



Order-Panels

Pyelonephritis/Cystitis Antibiotics

✓ Accept

- Suspected pyelonephritis, febrile UTI, or age < 2 years old
 - IV ceftriaxone with step-down to PO cephalexin is 1st line with culture and sensitivity results demonstrating cefazolin susceptibility (MIC less than or equal to 16)
 - Treat for 10 days if < 2 years old
 - Treat for 7 days if over 2 years old
- Cystitis
 - Age < 12 years old: PO therapy with cephalexin is 1st line
 - If IV therapy required, cefazolin is 1st line
 - Age 12 years old or greater: PO therapy with cephalexin or nitrofurantoin is 1st line
 - Treat for 5 days
- For allergy guidance see the antimicrobial handbook in Epic Resources, CHNO tab

☐ Pyelonephritis

☐ Cystitis

! Next Required

✓ Accept

Order-Panels

Antibiotics for Pneumonia

✓ Accept

Mild-Moderate:

- IV ampicillin with step-down to PO amoxicillin is 1st line for vaccinated (receipt of 2 or more HiB vaccines) patients
- IV ceftriaxone with step-down to PO amoxicillin/clavulanate is 1st line for unvaccinated (receipt of 1 or less HiB vaccines) patients
- Recommended Duration: 5-7 days

Severe:

- IV ceftriaxone AND vancomycin are recommended patients requiring ICU level care, moderate-large parapneumonic effusions, or signs of necrotizing pneumonia

Atypical Pneumonia

- Consider atypical pneumonia in patients 5 years old and above with risk factors (see CAP pathway)
- Azithromycin is 1st line for atypical organism coverage

For penicillin allergy guidance see the antimicrobial handbook in the resources, CHNO tab

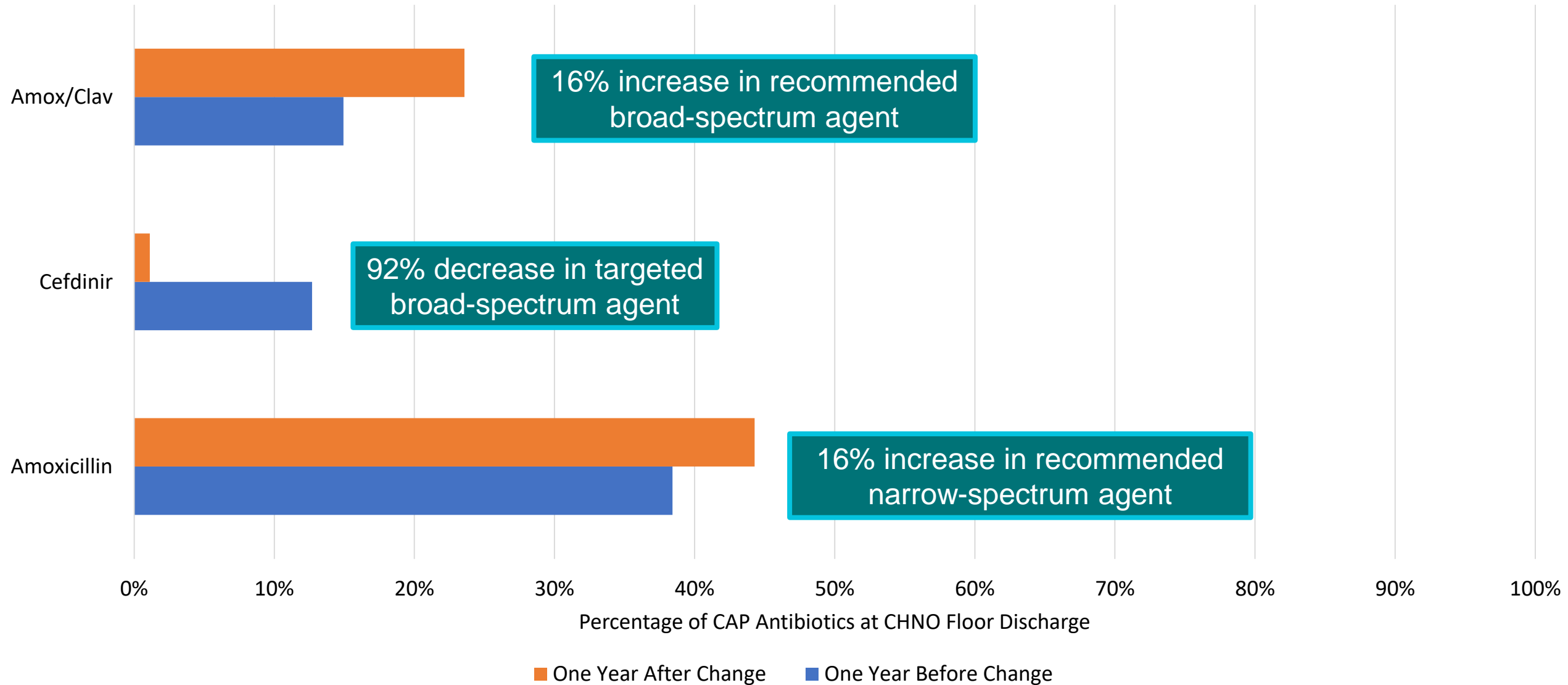
☐ IV Antibiotics

☐ Oral Antibiotics

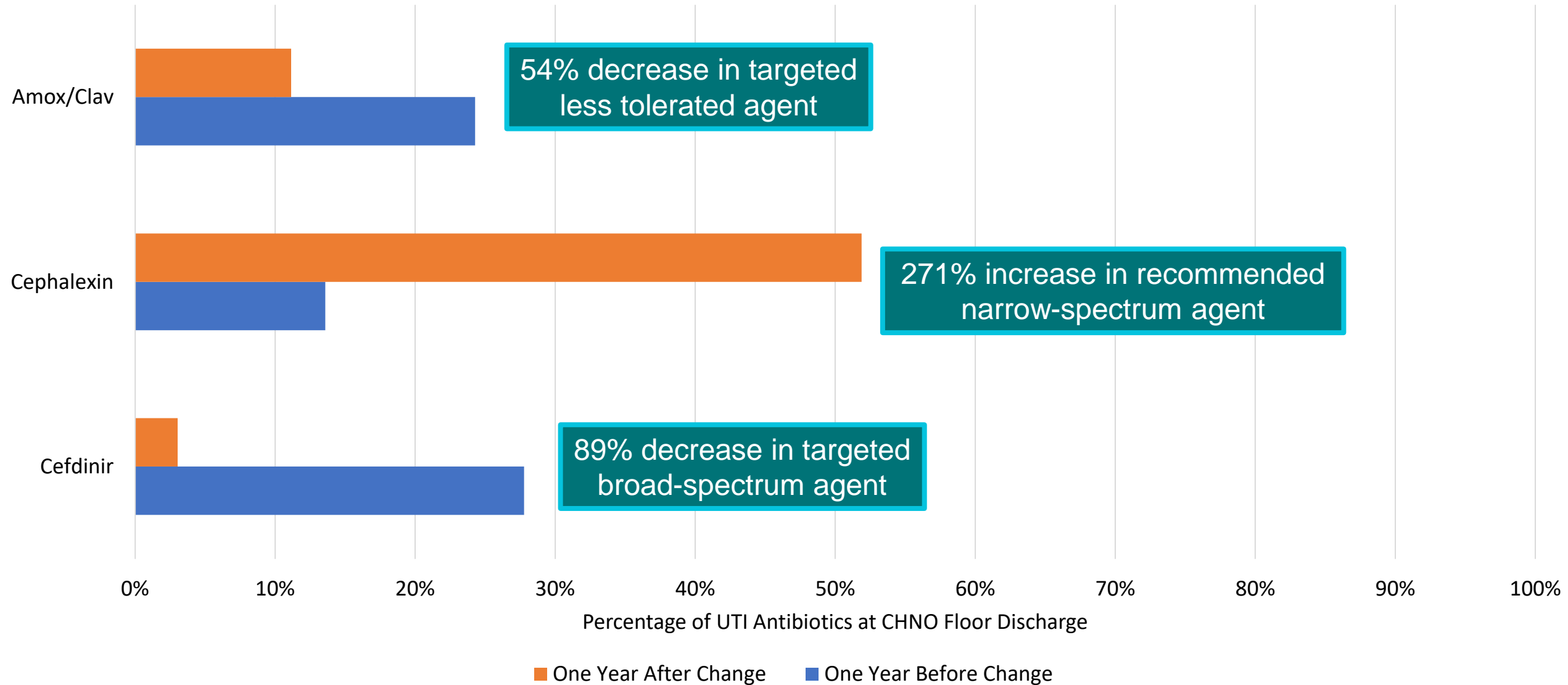
ⓘ Next Required

✓ Accept

CAP – Change Made Q3 2019



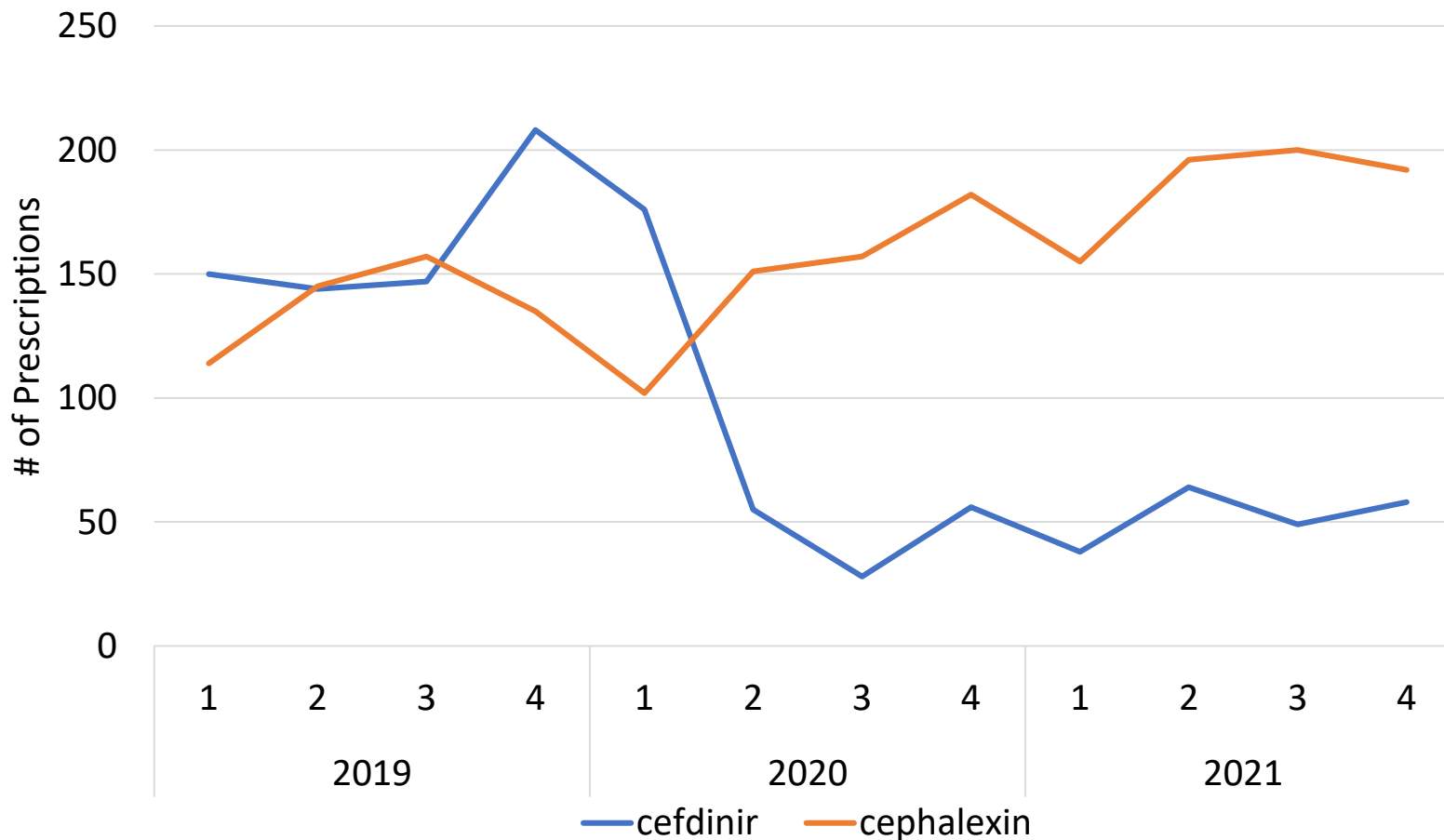
Pyelonephritis – Change Made Q1 2020



What About the ED? - UTI

Current data platform does not work for the ED for indication-specific data, but can determine total prescriptions by antibiotic

Total Rx # for Cefdinir and Cephalexin



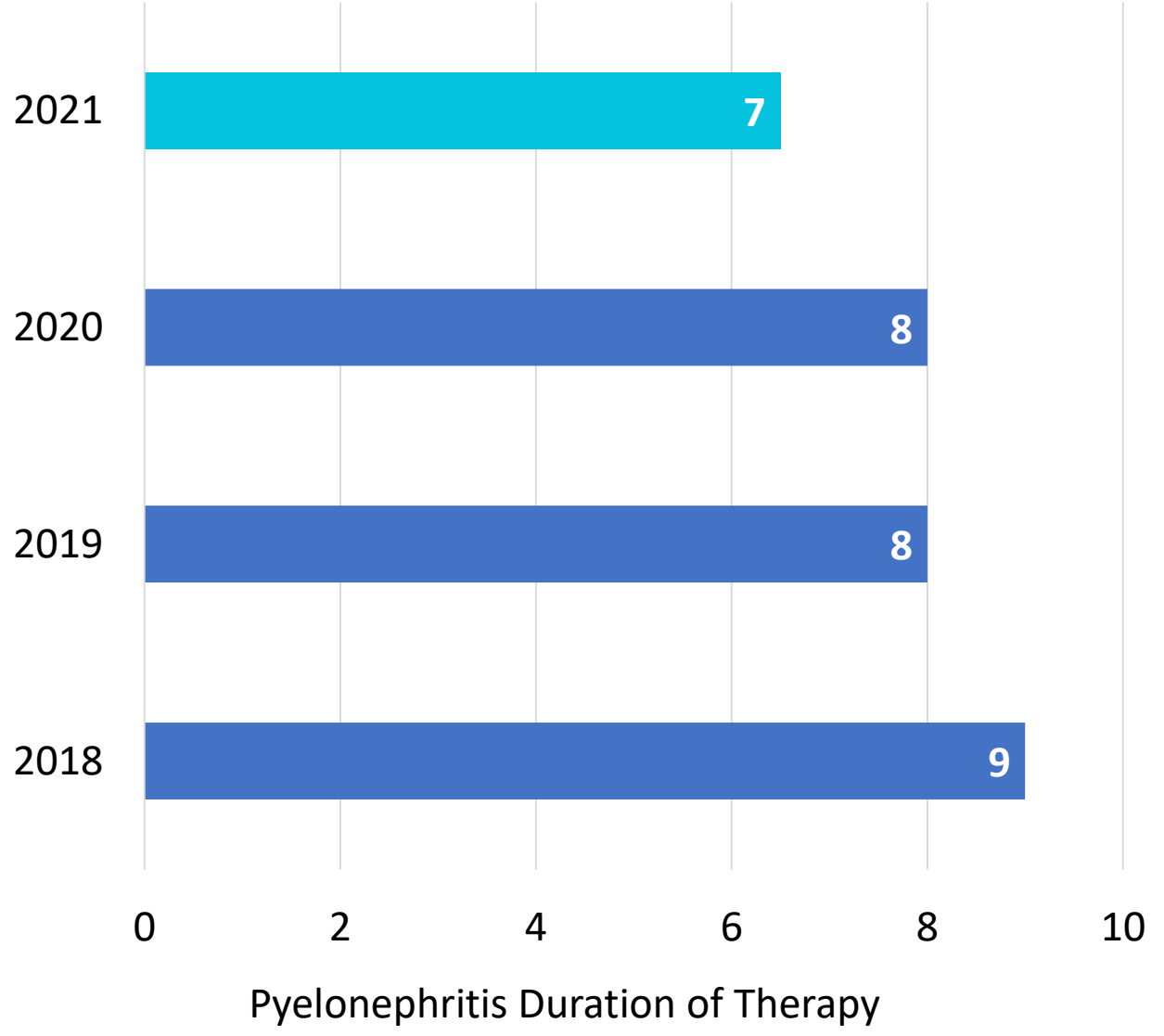
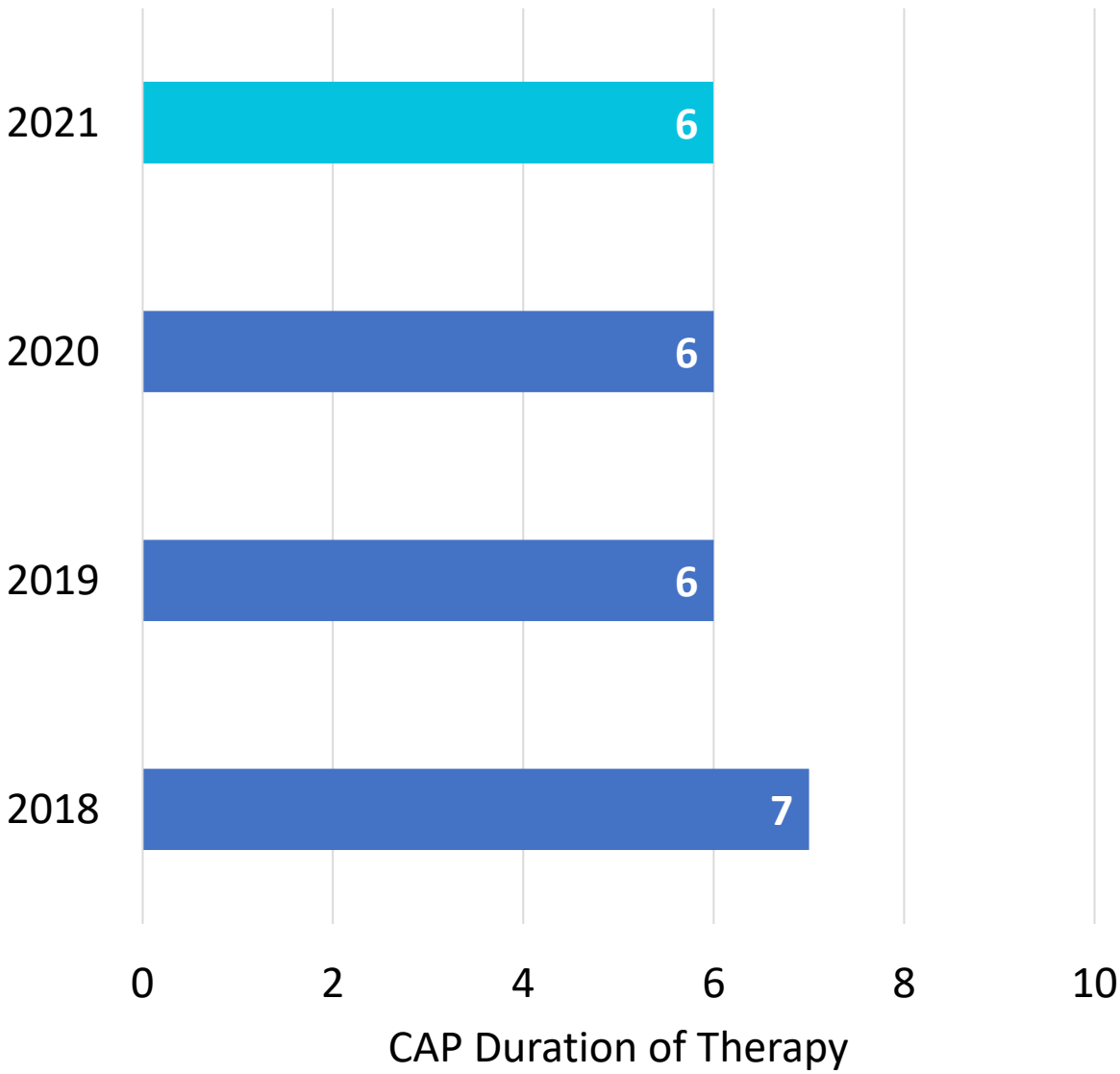
Flaws in this data:

- Not benchmarked to visits
- COVID significantly changed patient population during this time

Regardless:

- Cefdinir decreased
- Cephalexin increased
- Likely a change in practice

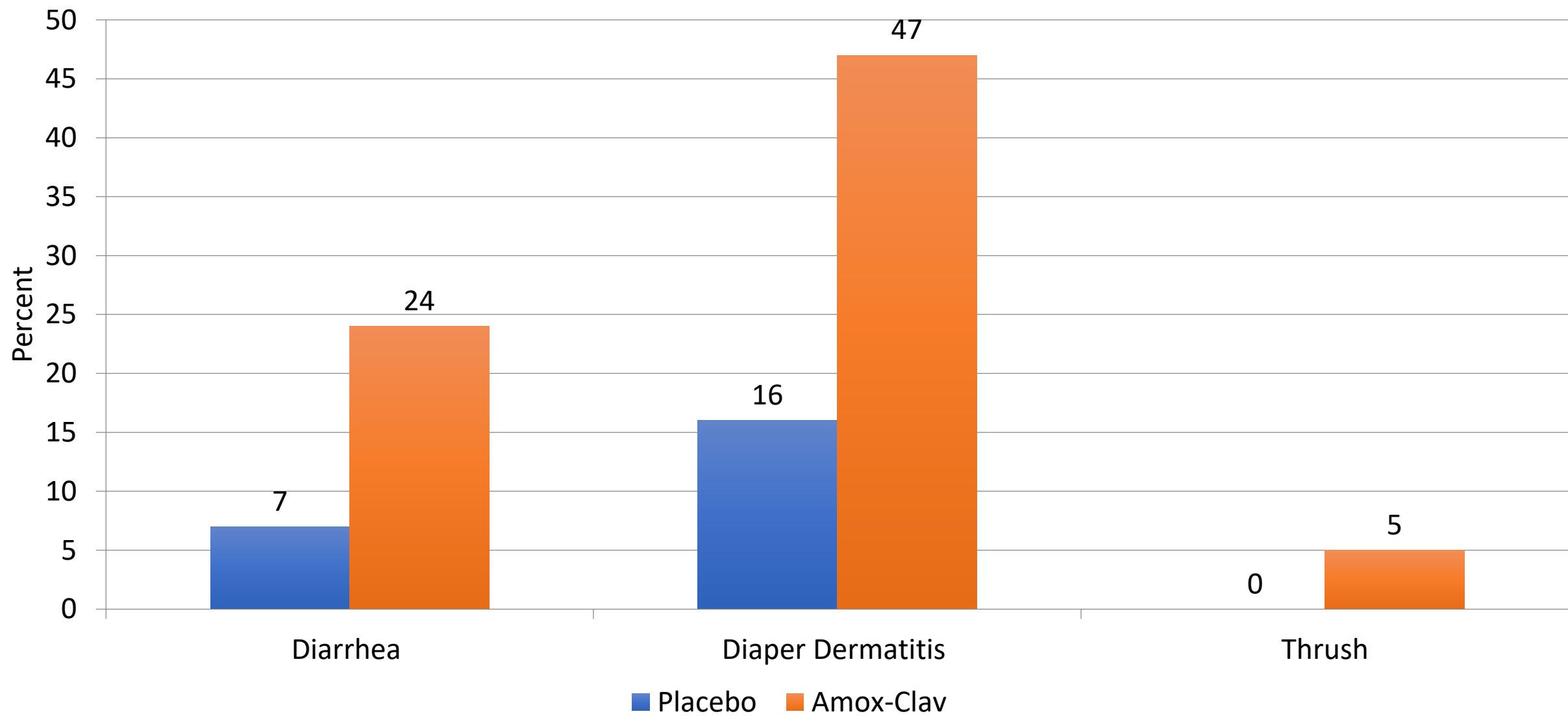
Durations of Therapy



Making Amox-Clav as Tolerable as Possible

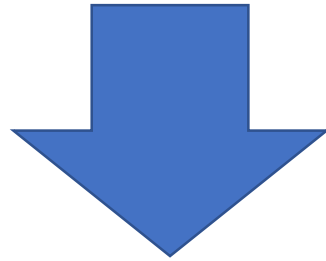
- Amox/Clav has many formulations with varying ratios of amoxicillin to clavulanate
→ CONFUSING!
- *S.pneumoniae* needs more amoxicillin, “high-dose”
 - Increased amoxicillin to clavulanate ratios are preferred for this (14:1 vs 7:1)
 - If non-ES formulations, 7:1, are used for “high-dose”, additional clavulanate causes diarrhea
- Downstream avoidance and increased oral 3GCs

Amoxicillin-Clavulanate vs Placebo



How to Order Amox/Clav




- Know infection is a “high-dose” infection and *S. pneumoniae* coverage is needed
- Know formulations of amox/clav and which formulations have less clav
- Pick from this list of products

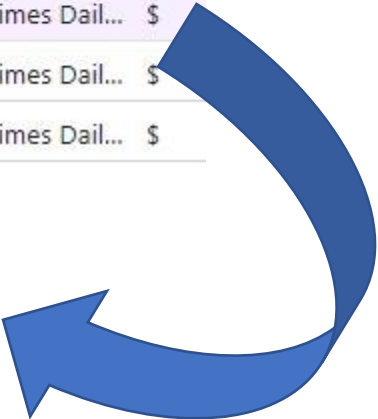


	amoxicillin-clavulanate (AUGMENTIN) suspension 250-62.5...		Oral	2 Times Dail...	\$	250-62.5 mg/5 mL
	amoxicillin-clavulanate (AUGMENTIN) suspension 400-57 m...		Oral	2 Times Dail...	\$	400-57 mg/5 mL
	amoxicillin-clavulanate (AUGMENTIN) tablet	250 mg of amoxicillin	Oral	3 Times Dail...		
	amoxicillin-clavulanate (AUGMENTIN) tablet 250-125 mg	250 mg of amoxicillin	Oral	3 Times Dail...		250-125 mg
	amoxicillin-clavulanate (AUGMENTIN) tablet 500-125 mg	500 mg of amoxicillin	Oral	3 Times Dail...	\$	500-125 mg
	amoxicillin-clavulanate (AUGMENTIN) tablet 875-125 mg	875 mg of amoxicillin	Oral	2 Times Dail...	\$	875-125 mg
	amoxicillin-clavulanate (AUGMENTIN-ES) suspension 600-4...		Oral	2 Times Dail...	\$	600-42.9 mg/5 mL

Order-Panels can Fix This

	amoxicillin-clavulanate (AUGMENTIN) suspension 250-62.5...		Oral	2 Times Dail...	\$
	amoxicillin-clavulanate (AUGMENTIN) suspension 400-57 m...		Oral	2 Times Dail...	\$
	amoxicillin-clavulanate (AUGMENTIN) tablet	250 mg of amoxicillin	Oral	3 Times Dail...	
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	amoxicillin-clavulanate (AUGMENTIN) tablet 875-125 mg	875 mg of amoxicillin	Oral	2 Times Dail...	\$
	amoxicillin-clavulanate (AUGMENTIN-ES) suspension 600-4...		Oral	2 Times Dail...	\$

	Amoxicillin-clavulanate (AUGMENTIN) Suspension				
	amoxicillin-clavulanate (AUGMENTIN) tablet 500-125 mg	500 mg of amoxicillin	Oral	3 Times Daily...	
	amoxicillin-clavulanate (AUGMENTIN) tablet 875-125 mg	875 mg of amoxicillin	Oral	2 Times Daily...	



Order-Panel

- Suspension order-panel asks indication first, and automatically links to preferred formulation and dosage based on age and weight of patient

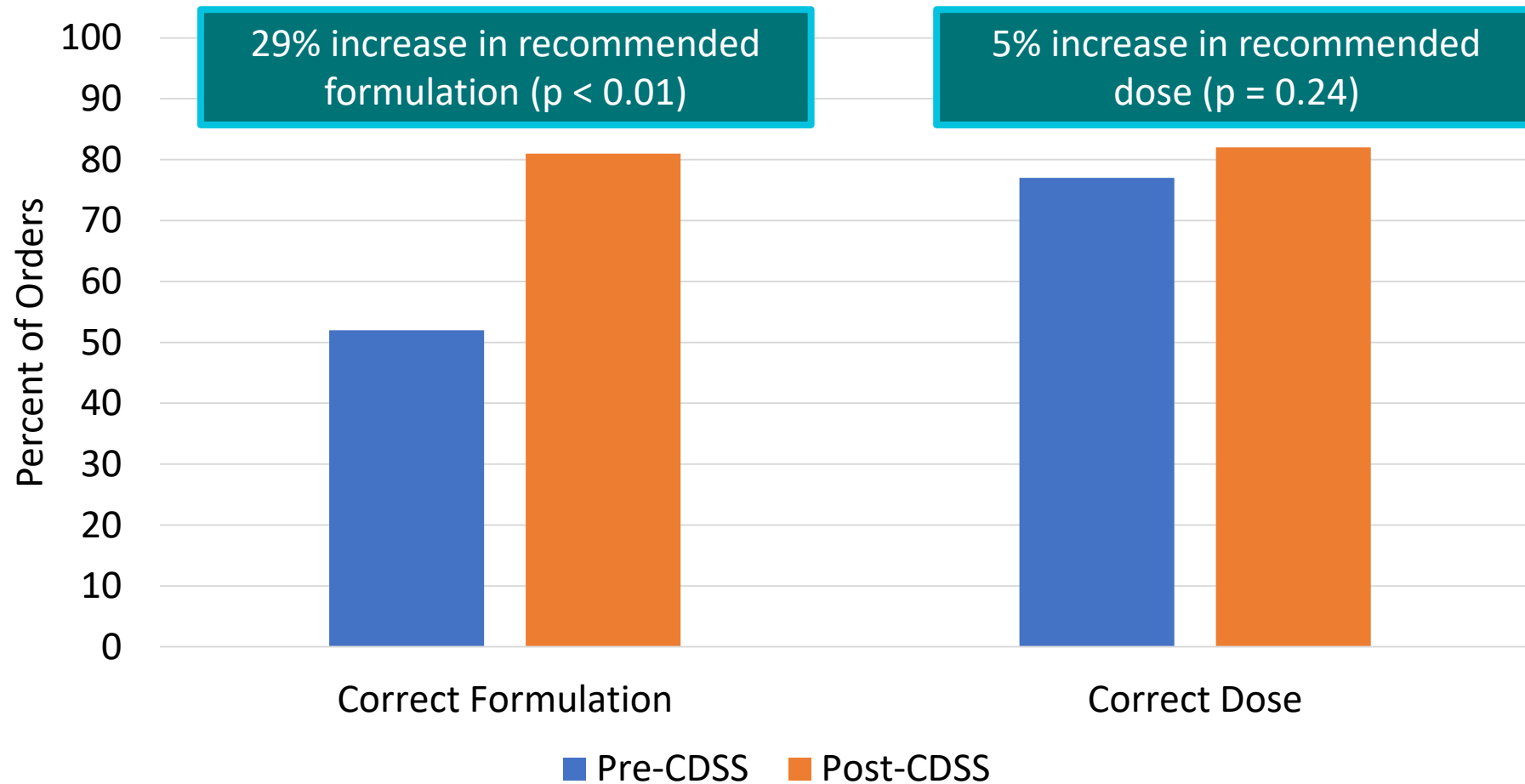
AMOXICILLIN-CLAVULANATE SUSPENSION (CHNO)

☐ High-Dose Indication (CAP, Otitis Media, Sinusitis) (\$)
☐ Normal Dose Indication (\$)
☐ Neonatal Indication (\$)

Next Required

Accept

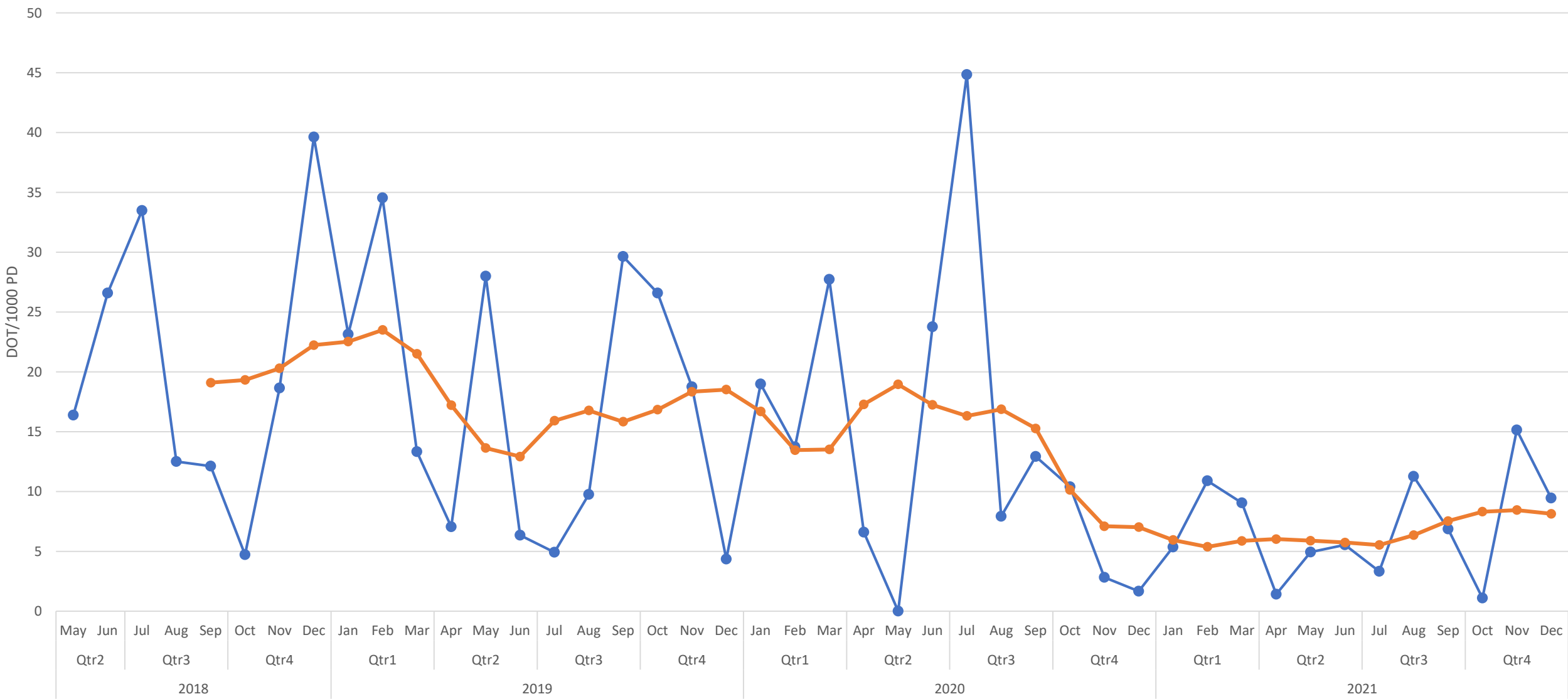
CDS Impact on Formulation and Dose Selection



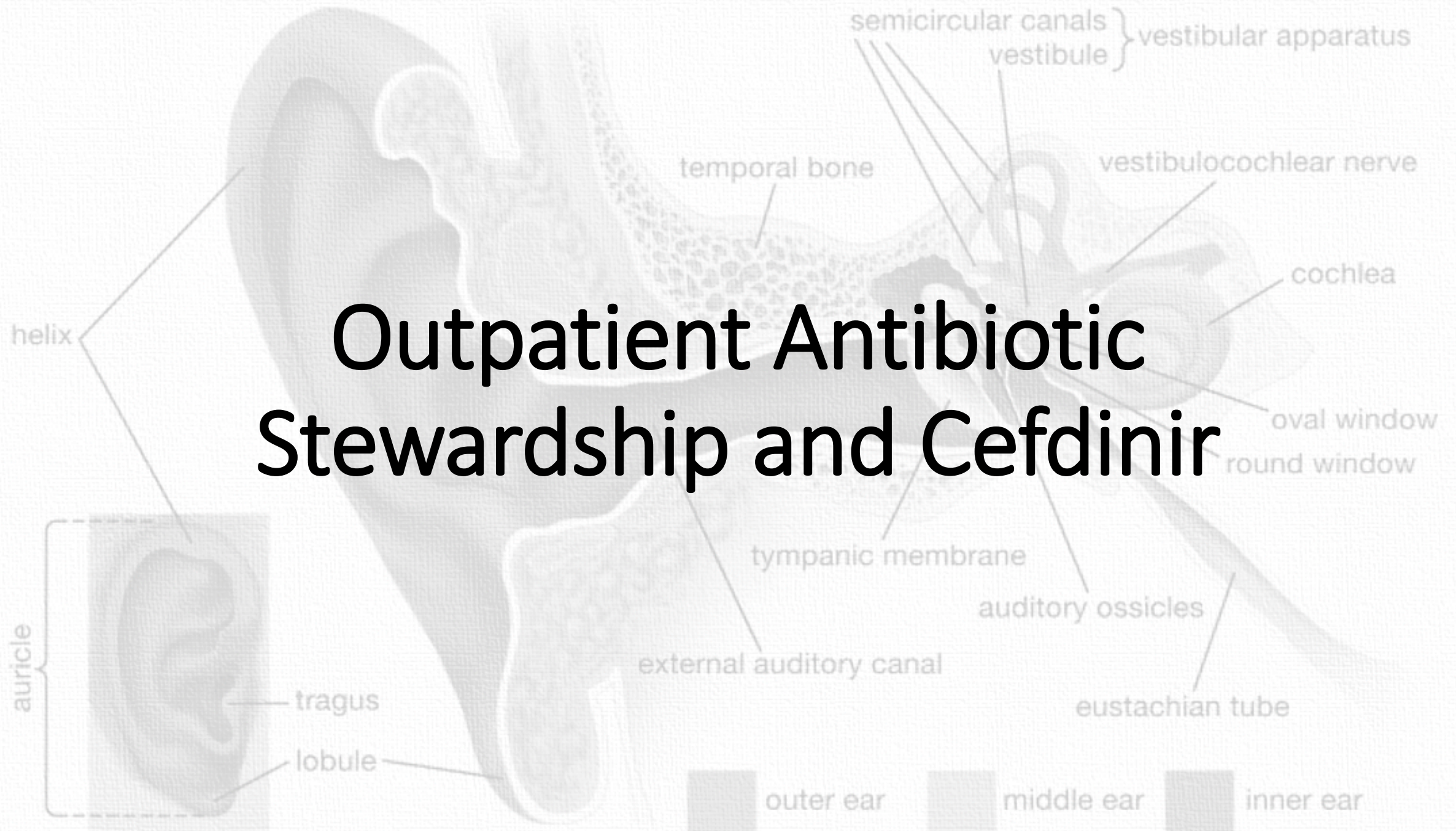
Formulation Changes

Suspension Formulations	Pre-CDSS n=151	Post-CDSS n=157	Difference
250-62.5 mg/5 mL	19 (13)	1 (0.6)	- 12%
400-57 mg/5 mL	59 (39)	68 (43)	+4%
600-42.9 mg/5 mL	73 (48)	88 (56)	+8%

Cefdinir DOT/1000 Days Present

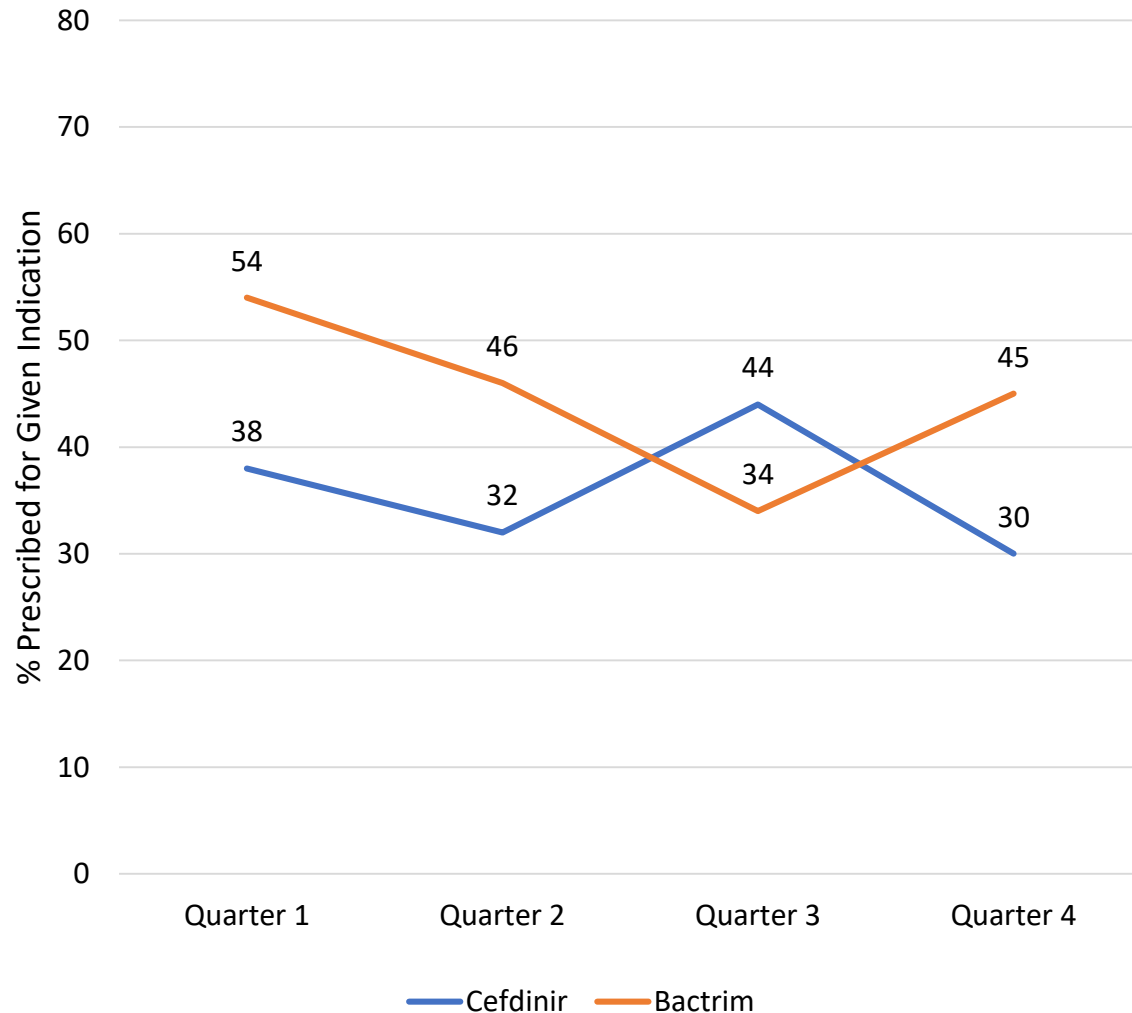


Outpatient Antibiotic Stewardship and Cefdinir

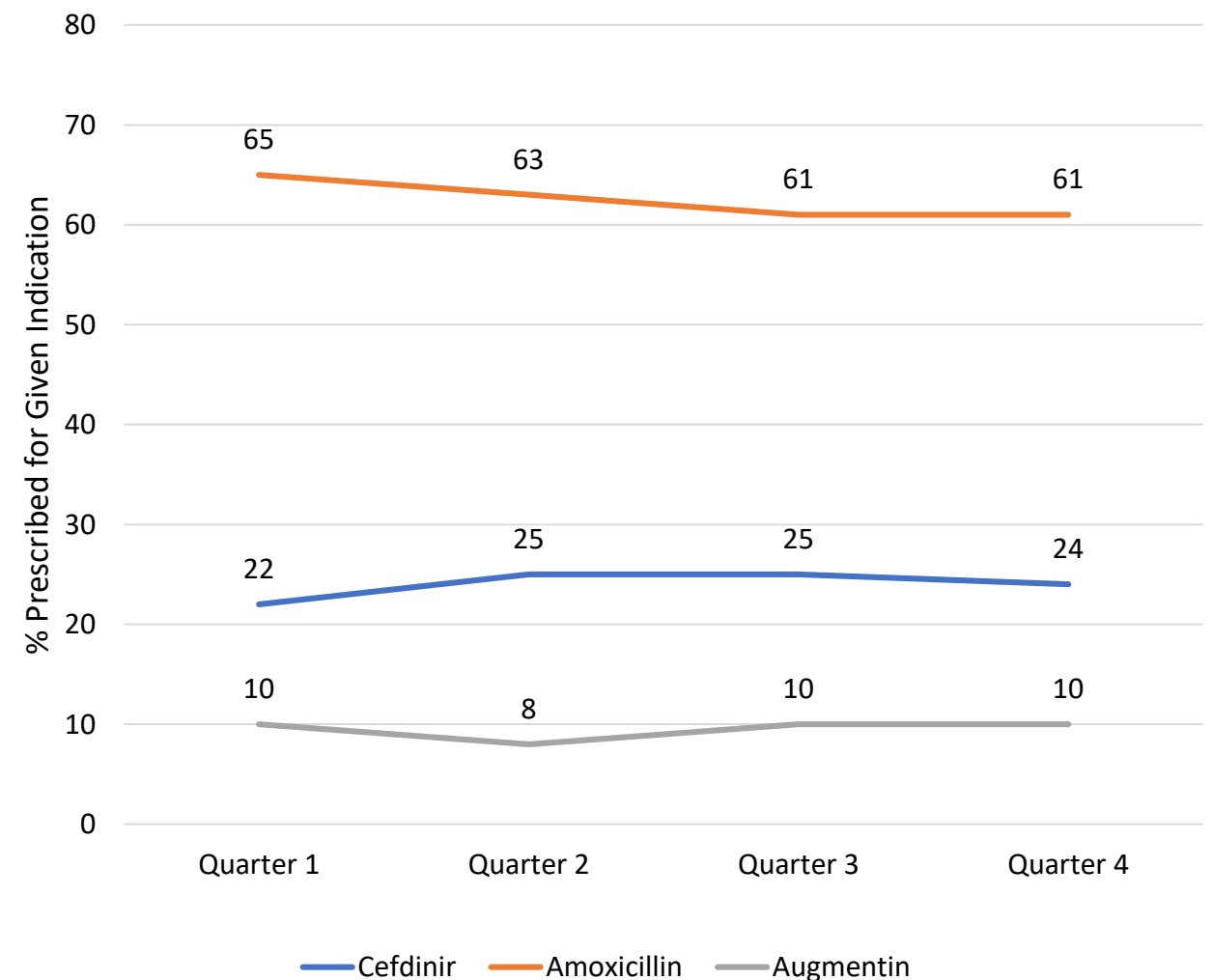


2021 CHMPC Rx Data – Which is the Worst ASP Issue ?

Rate of Antibiotic Prescription – UTI – CHMPC

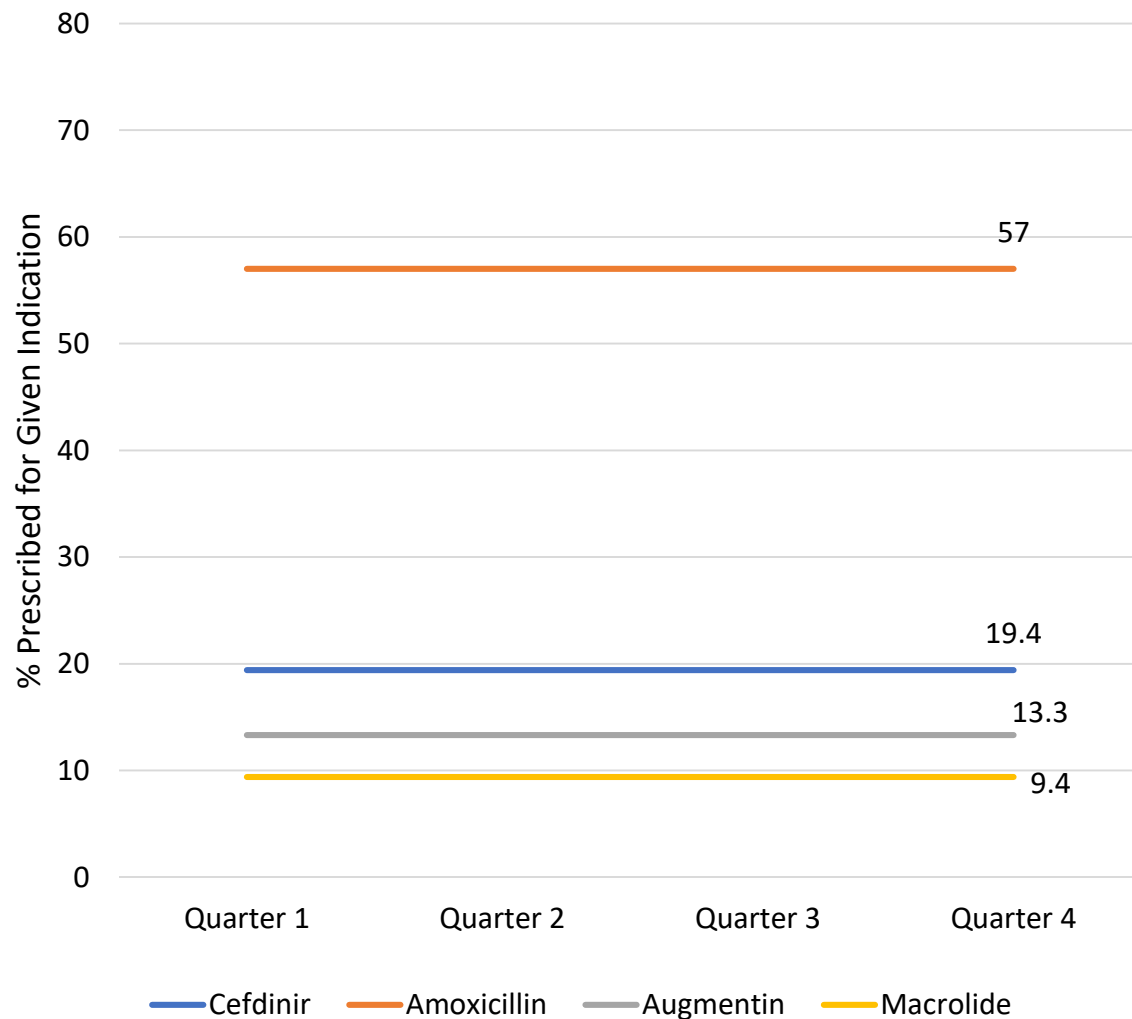


Rate of Antibiotic Prescription – AOM – CHMPC

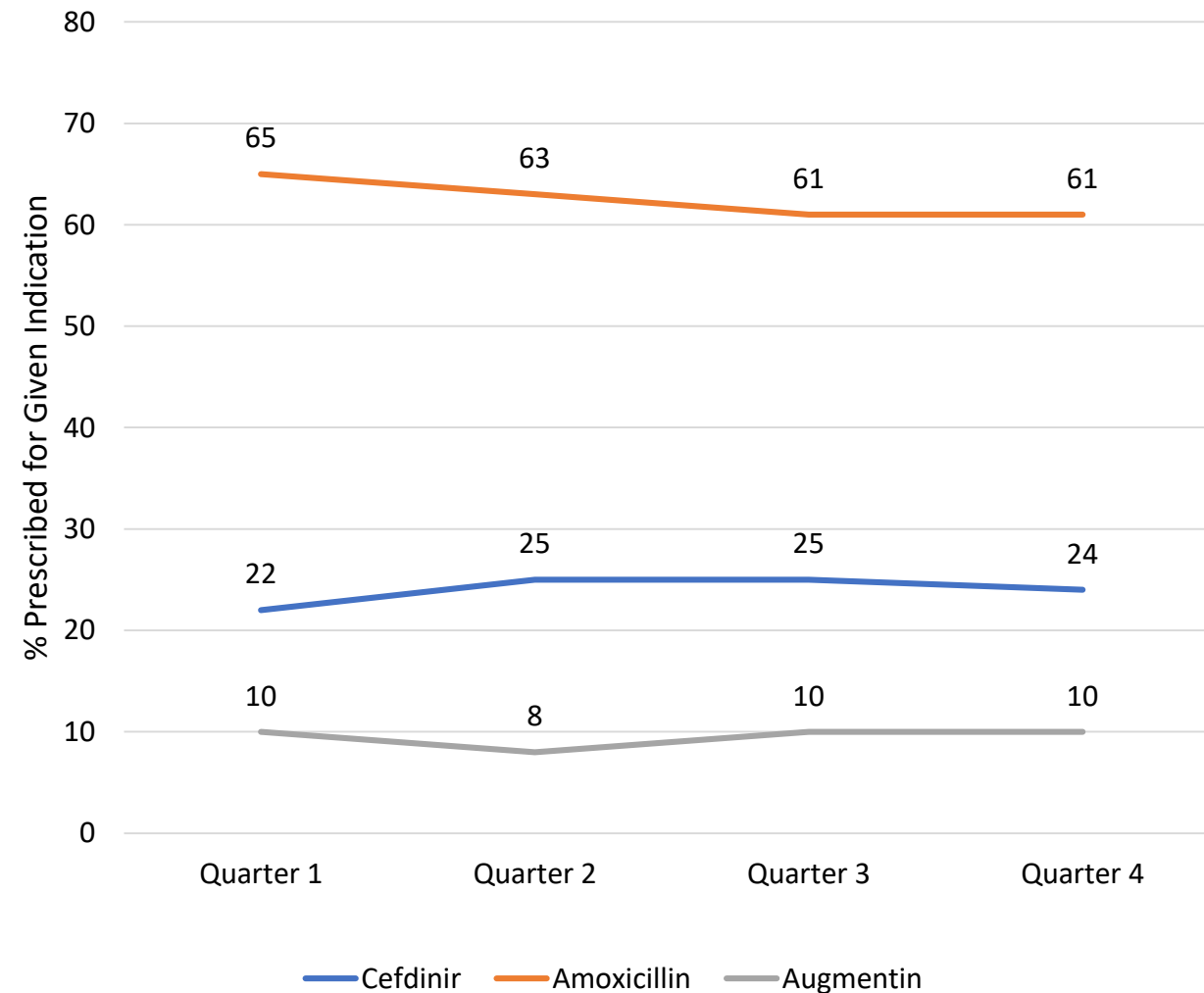


It Isn't Just Our Clinics

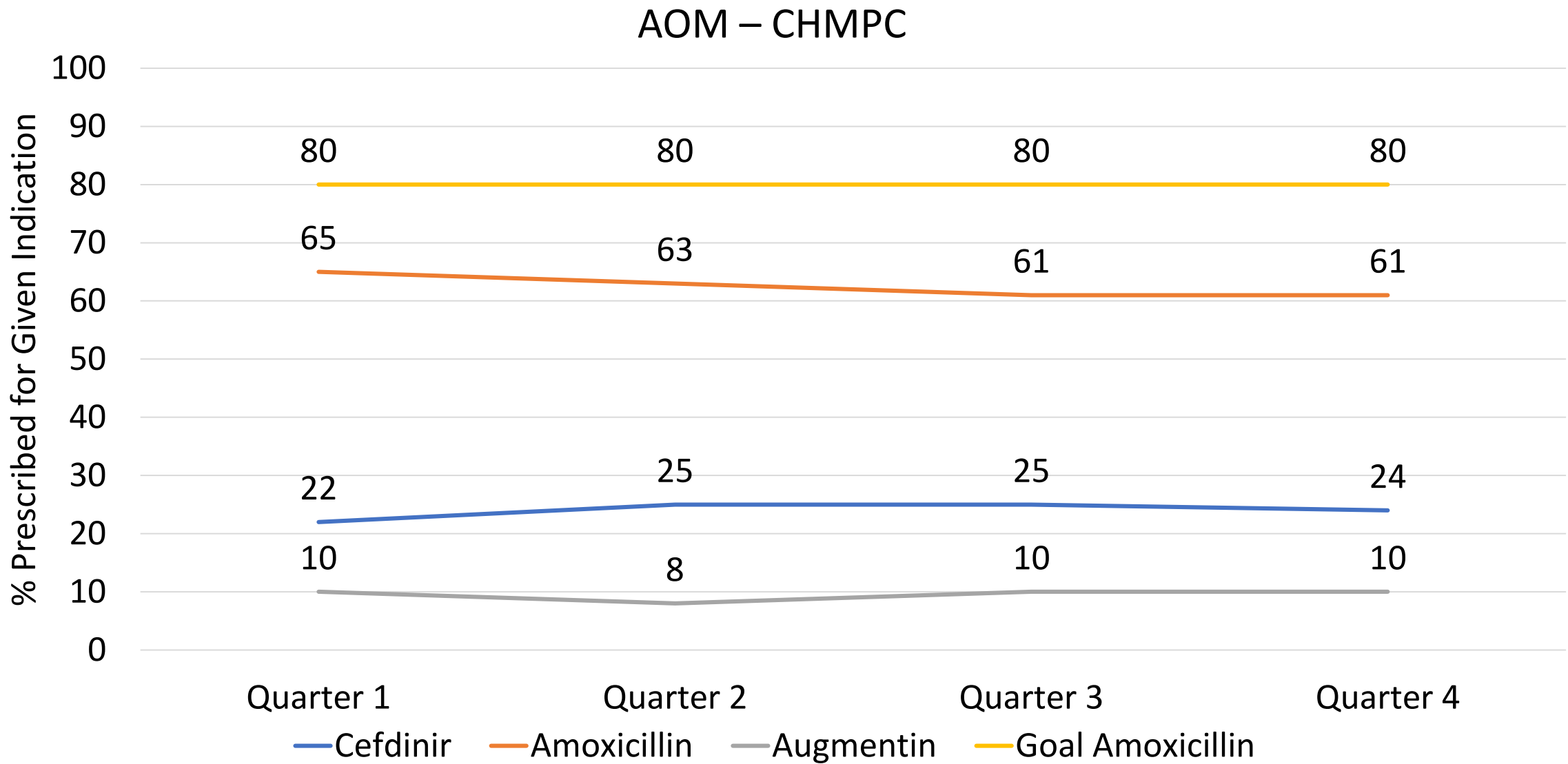
AOM – IBM Database



AOM – CHMPC

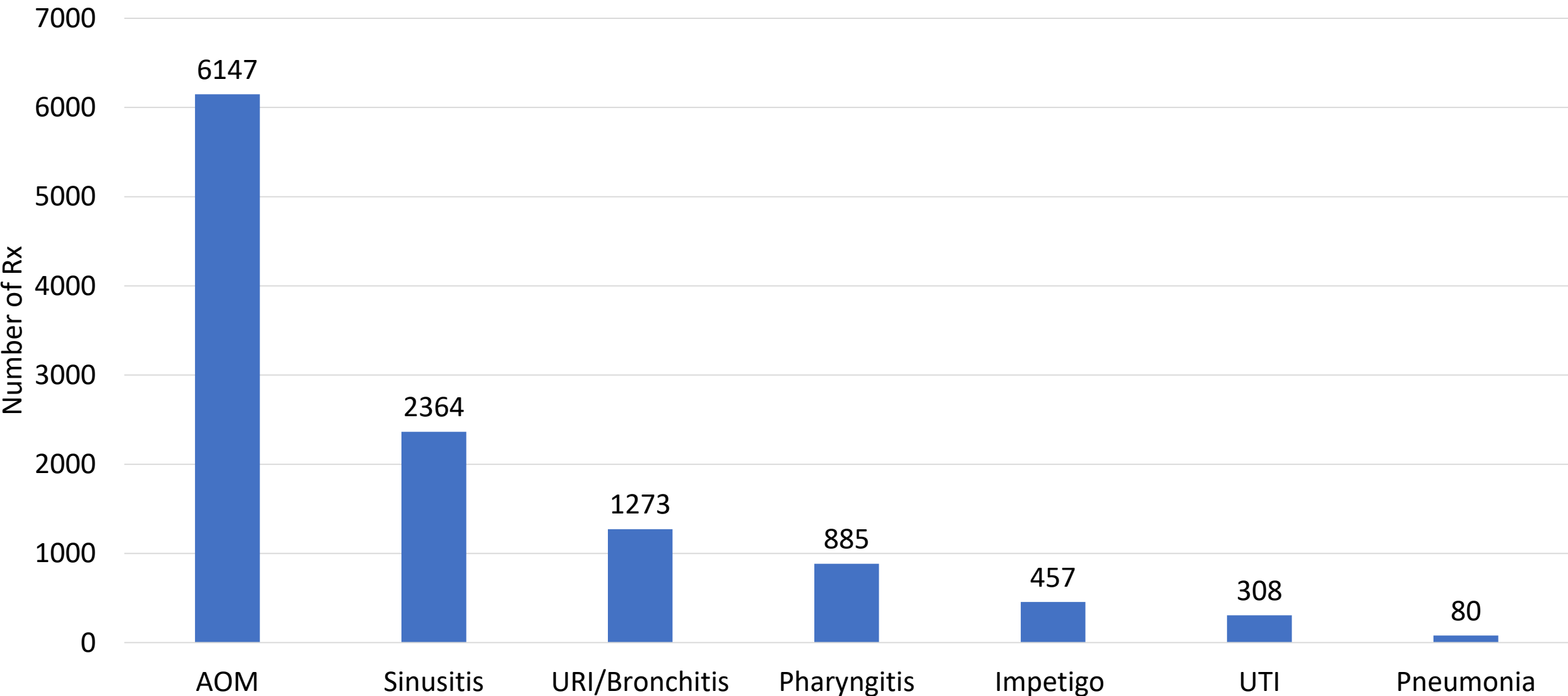


What Should be the Goal?

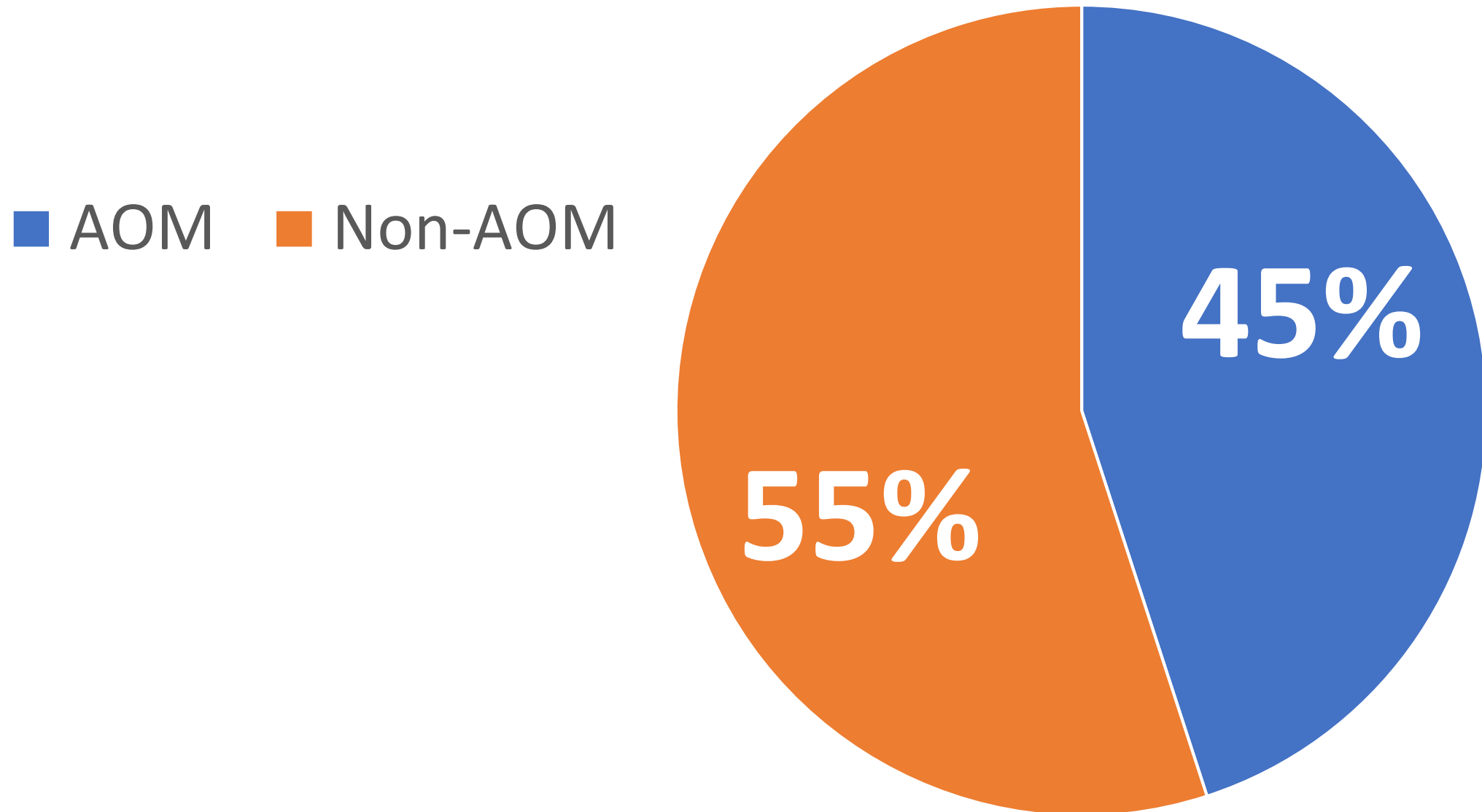


AOM is the Dominant Outpatient Antibiotic Indication

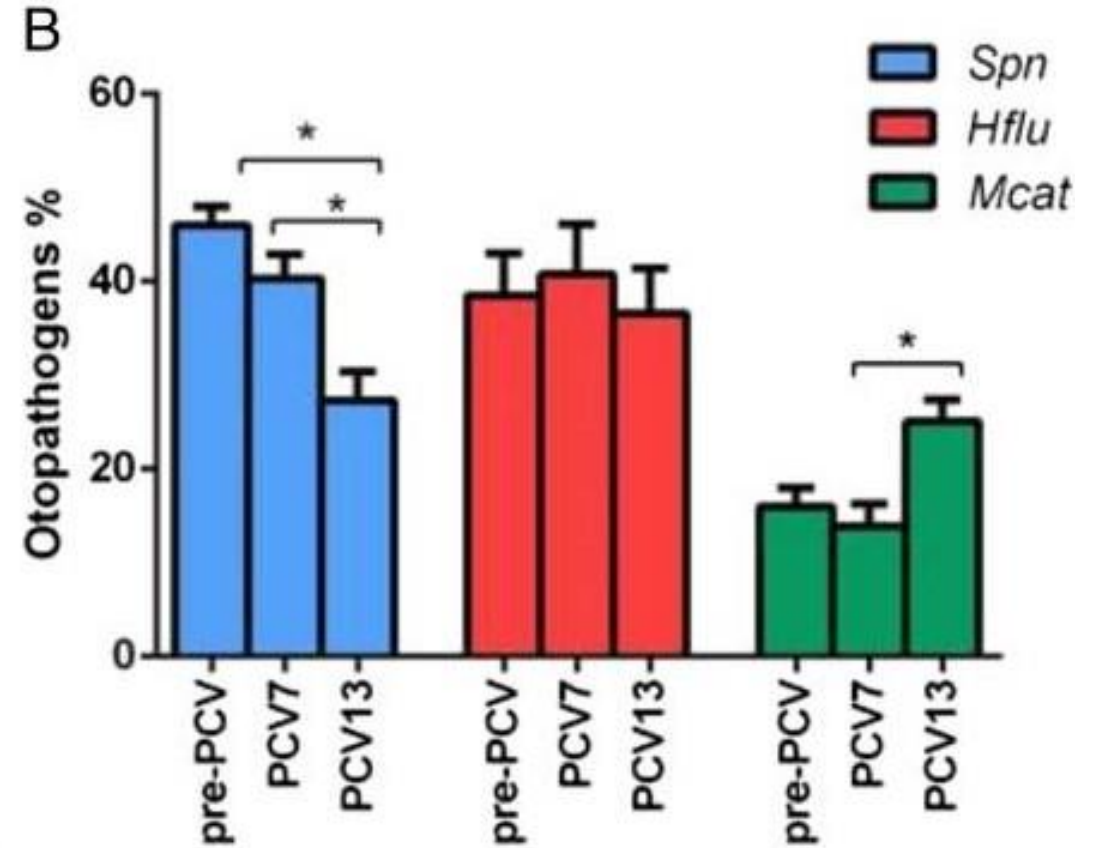
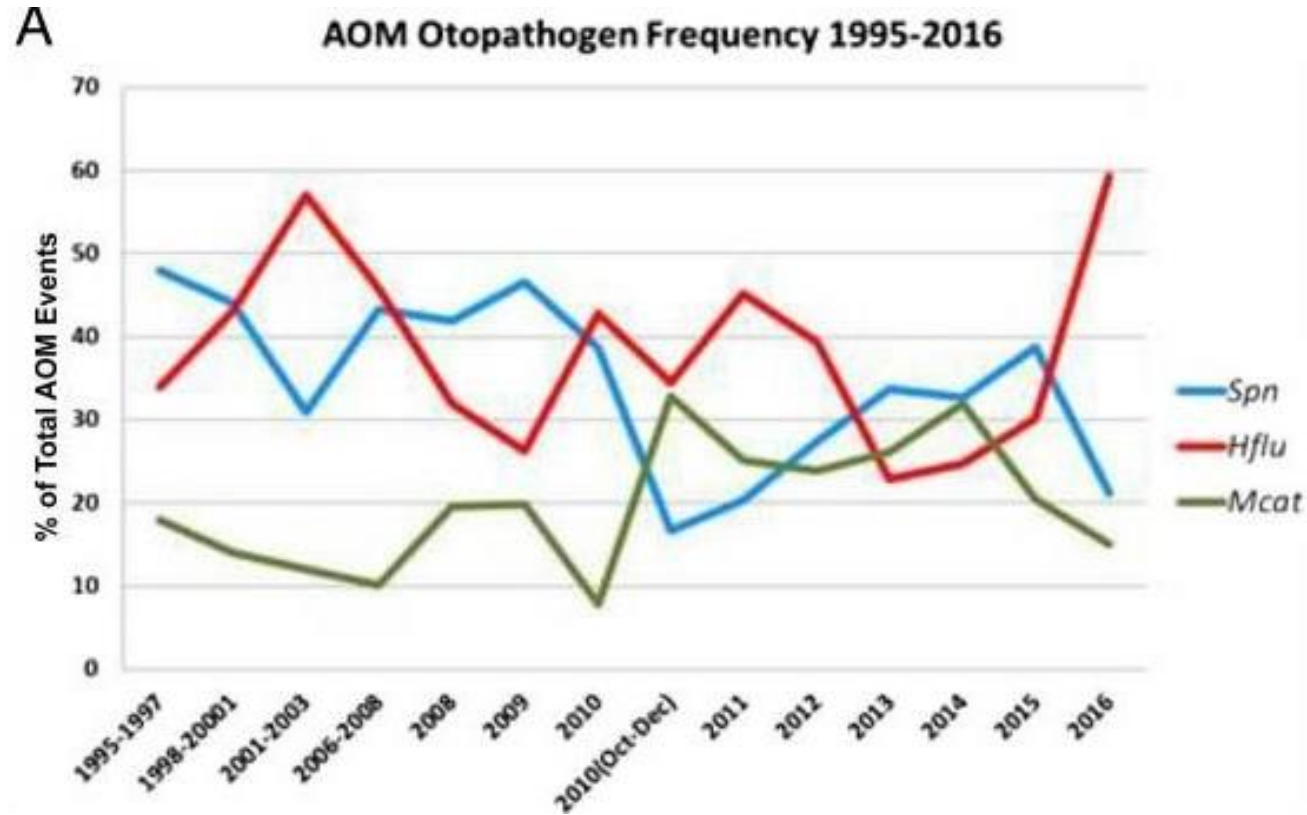
Number of Antibiotic Prescriptions for a Given Infection - CHMPC



AOM is the Dominant Outpatient Antibiotic Indication



Changing Otopathogen Frequency

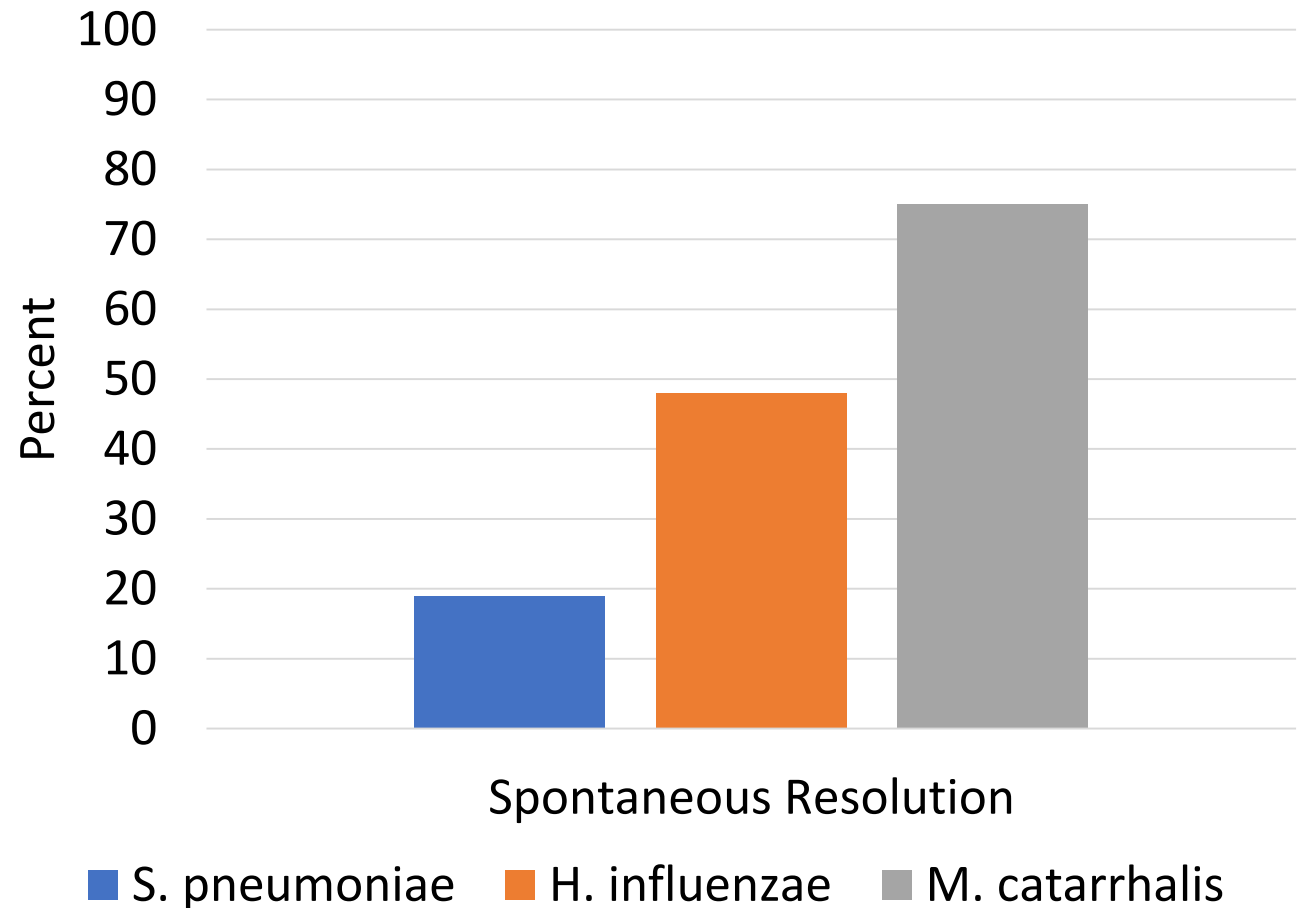


Why Amoxicillin Remains 1st Line

Antibiotics benefit
Streptococcus
pneumoniae the most

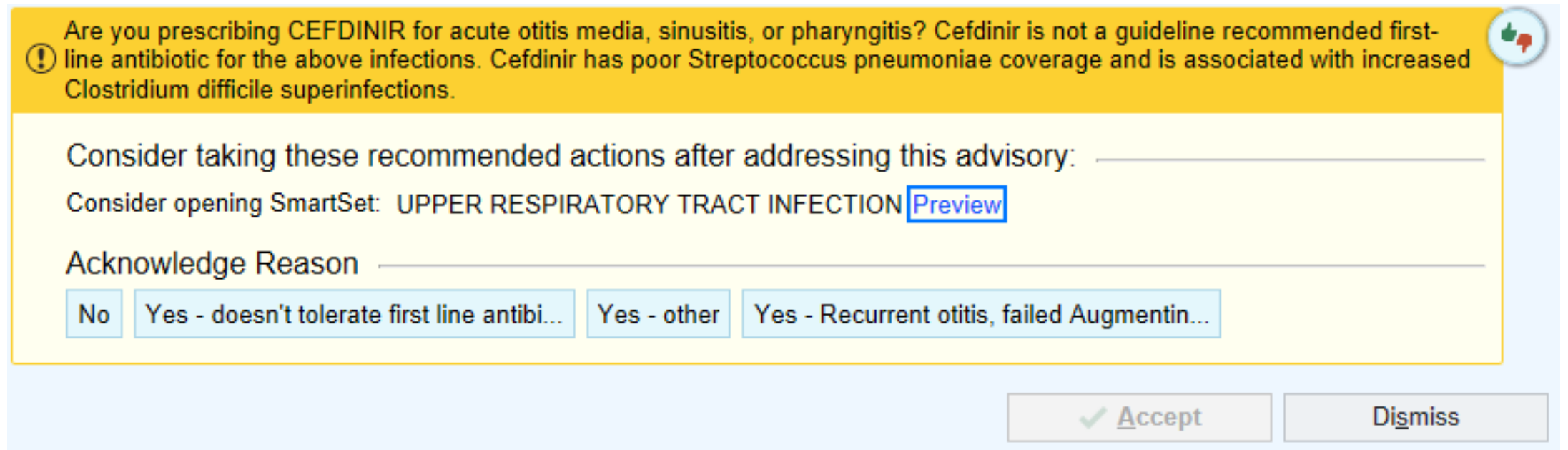
Number needed to
treat is rising in
vaccine era

Spontaneous Resolution of AOM by
Otopathogen



What's Next? Outpatient Projects

- Do best-practice alerts work in the outpatient setting?



Are you prescribing CEFDINIR for acute otitis media, sinusitis, or pharyngitis? Cefdinir is not a guideline recommended first-line antibiotic for the above infections. Cefdinir has poor *Streptococcus pneumoniae* coverage and is associated with increased *Clostridium difficile* superinfections.

Consider taking these recommended actions after addressing this advisory: _____

Consider opening SmartSet: UPPER RESPIRATORY TRACT INFECTION [Preview](#)

Acknowledge Reason _____

- Provider comparisons